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| NEWS 1 | | Web Page for STN Seminar Schedule - N. America |
| NEWS 2 | APR 04 | STN AnaVist, Version 1, to be discontinued |
| NEWS 3 | APR 15 | WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats |
| NEWS 4 | APR 28 | EMBASE Controlled Term thesaurus enhanced |
| NEWS 5 | APR 28 | IMSRESEARCH reloaded with enhancements |
| NEWS 6 | MAY 30 | INPAFAMDB now available on STN for patent family searching |
| NEWS 7 | MAY 30 | DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option |
| NEWS 8 | JUN 06 | EPFULL enhanced with 260,000 English abstracts |
| NEWS 9 | JUN 06 | KOREAPAT updated with 41,000 documents |
| NEWS 10 | JUN 13 | USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications |
| NEWS 11 | JUN 19 | CAS REGISTRY includes selected substances from web-based collections |
| NEWS 12 | JUN 25 | CA/CAplus and USPAT databases updated with IPC reclassification data |
| NEWS 13 | JUN 30 | AEROSPACE enhanced with more than 1 million U.S. patent records |
| NEWS 14 | JUN 30 | EMBASE, EMBAL, and LEMBASE updated with additional options to display authors and affiliated organizations |
| NEWS 15 | JUN 30 | STN on the Web enhanced with new STN AnaVist Assistant and BLAST plug-in |
| NEWS 16 | JUN 30 | STN AnaVist enhanced with database content from EPFULL |
| NEWS 17 | JUL 28 | CA/CAplus patent coverage enhanced |
| NEWS 18 | JUL 28 | EPFULL enhanced with additional legal status information from the epoline Register |
| NEWS 19 | JUL 28 | IFICDB, IFIPAT, and IFIUDB reloaded with enhancements |
| NEWS 20 | JUL 28 | STN Viewer performance improved |
| NEWS 21 | AUG 01 | INPADOCDB and INPAFAMDB coverage enhanced |
| NEWS 22 | AUG 13 | CA/CAplus enhanced with printed Chemical Abstracts page images from 1967-1998 |
| NEWS 23 | AUG 15 | CAOLD to be discontinued on December 31, 2008 |
| NEWS 24 | AUG 15 | CAplus currency for Korean patents enhanced |
| NEWS 25 | AUG 25 | CA/CAplus, CASREACT, and IFI and USPAT databases enhanced for more flexible patent number searching |
| NEWS 26 | AUG 27 | CAS definition of basic patents expanded to ensure comprehensive access to substance and sequence information |
| NEWS 27 | SEP 18 | Support for STN Express, Versions 6.01 and earlier, to be discontinued |

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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specific topic.

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=> File .GERRY2MBCE
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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=> S siRNA (S) NIK AND pd<=20041130
   1 FILES SEARCHED...
L1           0 SIRNA (S) NIK AND PD<=20041130

=> S RNA (S) NIK AND pd<=20041130
   1 FILES SEARCHED...
L2          17 RNA (S) NIK AND PD<=20041130

=> DUP REM L2
PROCESSING COMPLETED FOR L2
L3            9 DUP REM L2 (8 DUPLICATES REMOVED)
                ANSWERS '1-4' FROM FILE MEDLINE
                ANSWER '5' FROM FILE BIOSIS
                ANSWERS '6-9' FROM FILE CAPLUS

=> D IBIB abs L31-9
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In a multifile environment, a format can only be used if it is valid
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individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):L3
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'L11' IS NOT A VALID FORMAT
'1-9' IS NOT A VALID FORMAT
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in at least one of the files. Refer to file specific help messages
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individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):Ti

L3 ANSWER 1 OF 9 MEDLINE on STN DUPLICATE 1
TI Genetic evidence for the essential role of beta-transducin
repeat-containing protein in the inducible processing of NF-kappa B2/p100.

=> D IBIb Abs L3 1-9

L3 ANSWER 1 OF 9 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2002325290 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11994270
TITLE: Genetic evidence for the essential role of beta-transducin repeat-containing protein in the inducible processing of NF-kappa B2/p100.
AUTHOR: Fong Abraham; Sun Shao-Cong
CORPORATE SOURCE: Department of Microbiology and Immunology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033, USA.
CONTRACT NUMBER: 1R01 AI45045 (United States NIAID)
SOURCE: The Journal of biological chemistry, (2002 Jun 21) Vol. 277, No. 25, pp. 22111-4. Electronic Publication: 2002-05-06.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 18 Jun 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 19 Jul 2002
AB Processing of the nf kappa b2 gene product p100 to generate p52 is an important step in NF-kappa B regulation. This step is regulated by a nonclassical NF-kappa B signaling pathway involving the NF-kappa B-inducing kinase (NIK). NIK induces p100 processing by triggering phosphorylation of specific C-terminal serines of p100. However, the downstream molecular events leading to p100 processing remain unclear. Here we show that NIK induced the physical recruitment of beta-transducin repeat-containing protein (beta-TrCP), a component of the SCF ubiquitin ligase complex, to p100. This event required the phosphorylation sites as well as the death domain of p100. Using the RNA interference technique, we demonstrated that beta-TrCP is essential for NIK -induced p100 ubiquitination and processing. Interestingly the constitutive processing of p100 mutants was independent of beta-TrCP. These results suggest that beta-TrCP is an essential component of NIK-induced p100 processing.

L3 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002179110 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11911360
TITLE: Highly conserved NIKS tetrapeptide is functionally essential in eukaryotic translation termination factor eRF1.
AUTHOR: Frolova Ludmila; Seit-Nebi Alim; Kisselev Lev
CORPORATE SOURCE: Engelhardt Institute of Molecular Biology, Moscow, Russia.
SOURCE: RNA (New York, N.Y.), (2002 Feb) Vol. 8, No. 2, pp. 129-36.
Journal code: 9509184. ISSN: 1355-8382.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 26 Mar 2002
Last Updated on STN: 19 Apr 2002
Entered Medline: 18 Apr 2002

AB Class-1 polypeptide chain release factors (RFs) play a key role in translation termination. Eukaryotic (eRF1) and archaeal class-1 RFs possess a highly conserved Asn-Ile-Lys-Ser (NIKS) tetrapeptide located at the N-terminal domain of human eRF1. In the three-dimensional structure, NIKS forms a loop between helices. The universal occurrence and exposed nature of this motif provoke the appearance of hypotheses postulating an essential role of this tetrapeptide in stop codon recognition and ribosome binding. To approach this problem experimentally, site-directed mutagenesis of the NIKS (positions 61-64) in human eRF1 and adjacent amino acids has been applied followed by determination of release activity and ribosome-binding capacity of mutants. Substitutions of Asn61 and Ile62 residues of the NIKS cause a decrease in the ability of eRF1 mutants to promote termination reaction in vitro, but to a different extent depending on the stop codon specificity, position, and nature of the substituting residues. This observation points to a possibility that Asn-Ile dipeptide modulates the specific recognition of the stop codons by eRF1. Some replacements at positions 60, 63, and 64 cause a negligible (if any) effect in contrast to what has been deduced from some current hypotheses predicting the structure of the termination codon recognition site in eRF1. Reduction in ribosome binding revealed for Ile62, Ser64, Arg65, and Arg68 mutants argues in favor of the essential role played by the right part of the NIKS loop in interaction with the ribosome, most probably with ribosomal RNA.

L3 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001225756 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11160844
TITLE: The NF-kappaB pathway in human endometrium and first trimester decidua.
AUTHOR: King A E; Critchley H O; Kelly R W
CORPORATE SOURCE: MRC Human Reproductive Sciences Unit, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh, EH3 9ET, UK.. A.E.King-1@sms.ed.ac.uk
SOURCE: Molecular human reproduction, (2001 Feb) Vol. 7, No. 2, pp. 175-83.
Journal code: 9513710. ISSN: 1360-9947.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104

ENTRY DATE: Entered STN: 2 May 2001
Last Updated on STN: 19 Sep 2002
Entered Medline: 26 Apr 2001

AB Nuclear factor kappa B (NF-kappaB) regulates proinflammatory genes and may be involved in inflammation associated with reproductive events e.g. menstruation, implantation. Activation of NF-kappaB involves several protein kinases and subsequent degradation of an endogenous inhibitor, IkappaBalpha. This study details expression of NF-kappaB pathway intermediates in human endometrium and first trimester decidua. Messenger RNA was detected for IkappaBalpha, and IkappaB kinase gamma (IKKgamma, a scaffolding protein) and the protein kinases, IKKalpha, IKKbeta, NF-kappaB inducing kinase (NIK), mitogen-activated protein kinase Erk kinase kinase 1 (MEKK1) and TANK-binding kinase 1 (TBK1) using real-time quantitative polymerase chain reaction (PCR). IkappaBalpha and TBK1 mRNA were increased in the perimenstrual phase of the menstrual cycle. This suggests that there is activation of NF-kappaB due to premenstrual progesterone withdrawal, since NF-kappaB activity increases IkappaBalpha gene expression. Differential expression of NF-kappaB pathway intermediates occurred when progesterone concentrations increased in early pregnancy; IKKalpha and NIK mRNA levels increased in decidua whilst IKKbeta and MEKK1 mRNA levels declined. Expression profiles of IKKalpha and NIK proteins were determined immunohistochemically. Both were detected in glandular epithelium and endothelium of endometrium. In decidua, both were present in epithelium and decidualized stromal cells. The results of this study suggest that NF-kappaB is activated during menstruation. During early pregnancy, NF-kappaB may also be activated (via IKKalpha-NIK) and may regulate the expression of molecules vital for implantation and successful pregnancy. However, pro-inflammatory signalling to NF-kappaB (via IKKbeta-MEKK1) may be down-regulated in early pregnancy, contributing to the immunosuppressive mechanisms which prevail at this time.

L3 ANSWER 4 OF 9 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2000115862 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10648602
TITLE: Activation of the heterodimeric IkappaB kinase alpha (IKKalpha)-IKKbeta complex is directional: IKKalpha regulates IKKbeta under both basal and stimulated conditions.
AUTHOR: O'Mahony A; Lin X; Geleziunas R; Greene W C
CORPORATE SOURCE: Gladstone Institute of Virology and Immunology, Microbiology and Immunology, University of California, San Francisco, California 94141, USA.
CONTRACT NUMBER: P30A127763
SOURCE: Molecular and cellular biology, (2000 Feb) Vol. 20, No. 4, pp. 1170-8.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 29 Feb 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 15 Feb 2000

AB Signal-induced nuclear expression of the eukaryotic NF-kappaB transcription factor involves the stimulatory action of select mitogen-activated protein kinase kinase kinases on the IkappaB kinases (IKKalpha and IKKbeta) which reside in a macromolecular signaling complex termed the signalsome. While genetic studies indicate that IKKbeta is the

principal kinase involved in proinflammatory cytokine-induced IkappaB phosphorylation, the function of the equivalently expressed IKKalpha is less clear. Here we demonstrate that assembly of IKKalpha with IKKbeta in the heterodimeric signalsome serves two important functions: (i) in unstimulated cells, IKKalpha inhibits the constitutive IkappaB kinase activity of IKKbeta; (ii) in activated cells, IKKalpha kinase activity is required for the induction of IKKbeta. The introduction of kinase-inactive IKKalpha, activation loop mutants of IKKalpha, or IKKalpha antisense RNA into 293 or HeLa cells blocks NIK (NF-kappaB-inducing kinase)-induced phosphorylation of the IKKbeta activation loop occurring in functional signalsomes. In contrast, catalytically inactive mutants of IKKbeta do not block NIK-mediated phosphorylation of IKKalpha in these macromolecular signaling complexes. This requirement for kinase-proficient IKKalpha to activate IKKbeta in heterodimeric IKK signalsomes is also observed with other NF-kappaB inducers, including tumor necrosis factor alpha, human T-cell leukemia virus type 1 Tax, Cot, and MEKK1. Conversely, the theta isoform of protein kinase C, which also induces NF-kappaB/Rel, directly targets IKKbeta for phosphorylation and activation, possibly acting through homodimeric IKKbeta complexes. Together, our findings indicate that activation of the heterodimeric IKK complex by a variety of different inducers proceeds in a directional manner and is dependent on the kinase activity of IKKalpha to activate IKKbeta.

L3 ANSWER 5 OF 9 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:495837 BIOSIS
DOCUMENT NUMBER: PREV200000495958
TITLE: The nuclear factor kappa B pathway in human endometrium and first trimester decidua.
AUTHOR(S): King, A. E. [Reprint author]; Critchley, H. O. D. [Reprint author]; Kelly, R. W. [Reprint author]
CORPORATE SOURCE: MRC Human Reproductive Sciences Unit and Obstetrics and Gynaecology, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh, EH3 9ET, UK
SOURCE: Journal of Reproduction and Fertility Abstract Series, ( July, 2000) No. 25, pp. 66-67. print.
Meeting Info.: Joint Summer Meeting of the Society for the Study of Fertility, the British Andrology Society and the British Fertility Society. Edinburgh, Scotland, UK. July, 2000.
ISSN: 0954-0725.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Nov 2000
Last Updated on STN: 10 Jan 2002

L3 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1086770 CAPLUS
DOCUMENT NUMBER: 142:173862
TITLE: Identification and functional characterization of a novel human Misshapen/Nck interacting kinase-related kinase, hMINKβ
AUTHOR(S): Hu, Yuanming; Leo, Cindy; Yu, Simon; Huang, Betty C. B.; Wang, Hank; Shen, Mary; Luo, Ying; Daniel-Issakani, Sarkiz; Payan, Donald G.; Xu, Xiang
CORPORATE SOURCE: Rigel Pharmaceuticals, Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Biological Chemistry (2004), 279(52), 54387-54397
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular

Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Misshapen/NIKs-related kinase (MINK) is a member of the germinal center family of kinases that are homologous to the yeast sterile 20 (Ste20) kinases and regulate a wide variety of cellular processes, including cell morphol., cytoskeletal rearrangement, and survival. Here, we present the cloning and functional characterization of a novel human Misshapen/NIKs-related kinase β (hMINKβ) that encodes a polypeptide of 1312 amino acids. HMINKβ is ubiquitously expressed in most tissues with at least five alternatively spliced isoforms. Similar to Nck interacting kinase (NIK) and Traf2 and Nck-interacting kinase (TNIK), hMINKβ moderately activates c-Jun N-terminal kinase (JNK) and assocs. with Nck via the intermediate domain in the yeast two-hybrid system and in a glutathione S-transferase (GST) pull-down assay. Interestingly, overexpression of the kinase domain deleted and kinase-inactive mutants of hMINKβ in human fibrosarcoma HT1080 cells enhanced cell spreading, actin stress fiber formation, and adhesion to extracellular matrix, as well as decreased cell motility and cell invasion. Furthermore, these mutants also promoted cell-cell adhesion in human breast carcinoma MCF7 cells, evidenced with cell growth in clusters and increased membrane localization of β-catenin, a multifunctional protein involved in E-cadherin-mediated cell adhesion. Finally, hMINKβ protein was found to colocalize with the Golgi apparatus, implicating that hMINKβ might exert its functions, at least in part, through the modulation of intracellular protein transport. Taken together, these results suggest that hMINKβ plays an important role in cytoskeleton reorganization, cell adhesion, and cell motility.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:561174 CAPLUS
DOCUMENT NUMBER: 135:271044
TITLE: Activation of NF-κB by nontypeable Hemophilus influenzae is mediated by toll-like receptor 2-TAK1-dependent NIK-IKKα/β-IκBα and MKK3/6-p38 MAP kinase signaling pathways in epithelial cells
AUTHOR(S): Shuto, Tsuyoshi; Xu, Haidong; Wang, Beinan; Han, Jiahuai; Kai, Hirofumi; Gu, Xin-Xing; Murphy, Timothy F.; Lim, David J.; Li, Jian-Dong
CORPORATE SOURCE: Gonda Department of Cell and Molecular Biology, House Ear Institute and the Department of Otolaryngology, University of Southern California, Los Angeles, CA, 90057, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(15), 8774-8779
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nontypeable Hemophilus influenzae (NTHi) is an important human pathogen in both children and adults. In children, it causes otitis media, the most common childhood infection and the leading cause of conductive hearing loss in the United States. In adults, it causes lower respiratory tract infections in the setting of chronic obstructive pulmonary disease, the fourth leading cause of death in the United States. The mol. mechanisms underlying the pathogenesis of NTHi-induced infections remain undefined, but they may involve activation of NF-κB, a transcriptional activator of multiple host defense genes involved in immune and

inflammatory responses. Here, we show that NTHi strongly activates NF-κB in human epithelial cells via two distinct signaling pathways, NF-κB translocation-dependent and -independent pathways. The NF-κB translocation-dependent pathway involves activation of NF-κB inducing kinase (NIK)-IKKα/β complex leading to IκBα phosphorylation and degradation, whereas the NF-κB translocation-independent pathway involves activation of MKK3/6-p38 mitogen-activated protein (MAP) kinase pathway. Bifurcation of NTHi-induced NIK-IKKα/β-IκBα and MKK3/6-p38 MAP kinase pathways may occur at transforming growth factor-β activated kinase 1 (TAK1). Furthermore, we show that toll-like receptor 2 (TLR2) is required for NTHi-induced NF-κB activation. In addition, several key inflammatory mediators including IL-1β, IL-8, and tumor necrosis factor-α are up-regulated by NTHi. Finally, P6, a 16-kDa lipoprotein highly conserved in the outer membrane of all NTHi and H. influenzae type b strains, appears to also activate NF-κB via similar signaling pathways. Taken together, our results demonstrate that NTHi activates NF-κB via TLR2-TAK1-dependent NIK-IKKα/β-IκBα and MKK3/6-p38 MAP kinase signaling pathways. These studies may bring new insights into mol. pathogenesis of NTHi-induced infections and open up new therapeutic targets for these diseases.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:467814 CAPLUS

DOCUMENT NUMBER: 135:225811

TITLE: Activation of p38, ERK1/2 and NIK Pathways is Required for IL-1β and TNF-α-induced Chemokine Expression in Human Retinal Pigment Epithelial Cells

AUTHOR(S): Bian, Zong-Mei; Elner, Susan G.; Yoshida, Ayako; Kunkel, Steven L.; Su, Jia; Elner, Victor M.

CORPORATE SOURCE: Department of Ophthalmology, University of Michigan, Ann Arbor, MI, USA

SOURCE: Experimental Eye Research (2001), 73(1), 111-121
CODEN: EXERA6; ISSN: 0014-4835

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Chemokine secretion by human retinal pigment epithelium (hRPE) in response to IL-1β and TNF-α occurs in infectious and noninfectious retinal diseases. In this study, the roles of p38 kinase and extracellular signal-regulated kinase (ERK) signaling pathways were investigated for IL-1β- or TNF-α-induced IL-8 and MCP-1 secretion by hRPE cells. Treatment of hRPE cells with IL-1β or TNF-α caused increased steady-state IL-8 and MCP-1 mRNA levels and protein secretion. Stimulation of hRPE with IL-1β and TNF-α resulted in degradation of IκB-α, nuclear translocation of NF-κB, and prominent increases in p38 and ERK1/2 phosphorylation for as little as 3 min. The induced IL-8 and MCP-1 mRNA and proteins were partially suppressed by U0126, a specific MEK inhibitor, and by SB202190, a selective p38 inhibitor. This induction was completely blocked by simultaneous administration of the two drugs or by incubation with inhibitors for activation of NF-κB such as BAY11-7085, CAPE, and parthenolide. These results suggest that co-activation of MEK/ERK and p38 pathways as well as activation of NIK pathway are essential for IL-1β- and TNF-α-stimulation of IL-8 and MCP-1 gene expression in hRPE cells. Furthermore, co-administration of U0126 and SB202190 did not affect the induced degradation of IκB-α and NF-κB nuclear translocation, indicating that NF-κB is activated by IL-1β and TNF-α independently of activation of MEK/MAPK and p38

pathways in hRPE cells. (c) 2001 Academic Press.
REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:456596 CAPLUS
DOCUMENT NUMBER: 131:227457
TITLE: Differential IκB kinase activation and IκBα degradation by interleukin-1β and tumor necrosis factor-α in human U937 monocytic cells. Evidence for additional regulatory steps in κB-dependent transcription
AUTHOR(S): Nasuhara, Yasuyuki; Adcock, Ian M.; Catley, Matthew; Barnes, Peter J.; Newton, Robert
CORPORATE SOURCE: Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, SW3 6LY, UK
SOURCE: Journal of Biological Chemistry (1999), 274(28), 19965-19972
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The IκB kinases (IKKs) lie downstream of the NF-κB-inducing kinase (NIK) and activate NF-κB by phosphorylation of IκBα. This leads to IκBα degradation and release of NF-κB. In U937 monocytic cells, interleukin (IL)-1β (1 ng/mL) and tumor necrosis factor (TNF)-α (10 ng/mL) induced κB-dependent transcription equally. However, IKK activity was strongly induced by TNF-α but not by IL-1β. This was consistent with IκBα phosphorylation and degradation, yet TNF-α-induced NF-κB DNA binding was only 30-40% greater than for IL-1β. This was not explained by degradation of IκBβ, IκBε, or p105 nor nuclear translocation of NF-κB·IκBα complexes or degradation-independent release of NF-κB. Dominant neg. (NIK) repressed TNF-α and IL-1β-induced κB-dependent transcription by .apprx.60% and .apprx.35%, resp. These data reveal an imprecise relation between IKK activation, IκBα degradation, and NF-κB DNA binding, suggesting the existence of addnl. mechanisms that regulate NF-κB activation. Finally, the lack of correlation between DNA binding and transcriptional activation plus the fact that PP1 and genistein both inhibited κB-dependent transcription without affecting DNA binding activity demonstrate the existence of regulatory steps downstream of NF-κB DNA binding. Therapeutically these data are important as inhibition of the NIK-IKK-IκBα cascade may not produce equivalent redns. in NF-κB-dependent gene expression.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 17:20:39 ON 24 SEP 2008

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

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LOGINID:SSPTAEGS1646

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE'
AT 17:23:32 ON 24 SEP 2008
FILE 'MEDLINE' ENTERED AT 17:23:32 ON 24 SEP 2008
FILE 'BIOSIS' ENTERED AT 17:23:32 ON 24 SEP 2008
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FULL ESTIMATED COST                                      32.29      32.50

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -3.20      -3.20

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     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 17:16:47 ON 24 SEP 2008
L1             0 S SIRNA (S) NIK AND PD<=20041130
L2            17 S RNA (S) NIK AND PD<=20041130
L3             9 DUP REM L2 (8 DUPLICATES REMOVED)

=> S expression (S) (down-regulat? OR Inhibit?) (S) (NIK OR (NF-kappa B inducing
kinase)) AND pd<=20041130
   1 FILES SEARCHED...
   3 FILES SEARCHED...
L4           114 EXPRESSION (S) (DOWN-REGULAT? OR INHIBIT?) (S) (NIK OR (NF-KAPPA
                 B INDUCING KINASE)) AND PD<=20041130

=> Dup Rem L4
PROCESSING COMPLETED FOR L4
L5            45 DUP REM L4 (69 DUPLICATES REMOVED)
                 ANSWERS '1-24' FROM FILE MEDLINE
                 ANSWERS '25-32' FROM FILE BIOSIS
                 ANSWERS '33-42' FROM FILE CAPLUS
                 ANSWERS '43-45' FROM FILE EMBASE

=> D Ibib abs L5 1-24

L5   ANSWER 1 OF 45     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2004312280     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15090542
TITLE:              Protein farnesyltransferase inhibitor (SCH 66336) abolishes
                    NF-kappaB activation induced by various carcinogens and
                    inflammatory stimuli leading to suppression of
                    NF-kappaB-regulated gene expression and up-regulation of
                    apoptosis.
AUTHOR:             Takada Yasunari; Khuri Fadlo R; Aggarwal Bharat B
CORPORATE SOURCE:   Cytokine Research Laboratory, Department of
                    Bioimmunotherapy, The University of Texas M. D. Anderson
                    Cancer Center, Houston, Texas 77030, USA.
CONTRACT NUMBER:    P01-CA91844 (United States NCI)
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SOURCE: The Journal of biological chemistry, (2004 Jun 18) Vol. 279, No. 25, pp. 26287-99. Electronic Publication: 2004-04-16. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 25 Jun 2004 Last Updated on STN: 25 Jul 2004 Entered Medline: 23 Jul 2004

AB Ras farnesyltransferase inhibitor (FTI) exhibit antiproliferative and antiangiogenic effects through a mechanism that is poorly understood. Because of the known role of Ras in the activation of transcription factor NF-kappaB and because NF-kappaB-regulated genes can control cell survival and angiogenesis, we postulated that FTI mediates its effects in part by modulating NF-kappaB activation. Therefore, in the present study we investigated the effect of FTI, SCH 66336, on NF-kappaB and NF-kappaB-regulated gene expression activated by a variety of inflammatory and carcinogenic agents. We demonstrate by DNA-binding assay that NF-kappaB activation induced by tumor necrosis factor (TNF), phorbol 12-myristate 13-acetate, cigarette smoke, okadaic acid, and H(2)O(2) was completely suppressed by SCH 66336; the suppression was not cell type-specific. This FTI suppressed the activation of IkappaBalpha kinase (IKK), thus abrogating the phosphorylation and degradation of IkappaBalpha. Additionally, TNF-activated Ras and SCH 66336 inhibited the activation. Also, overexpression of Ras (V12) enhanced TNF-induced NF-kappaB activation, and adenoviral dominant-negative Ras (N17) suppressed the activation, thus suggesting the critical role of Ras in TNF signaling. SCH 66336 also inhibited the NF-kappaB-dependent reporter gene expression activated by TNF, TNFR1, TRADD, TRAF2, NIK, and IKK but not that activated by the p65 subunit of NF-kappaB. The TNF-induced NF-kappaB-regulated gene products cyclin D1, COX-2, MMP-9, survivin, IAP1, IAP2, XIAP, Bcl-2, Bfl-1/A1, TRAF1, and FLIP were all down-regulated by SCH 66336, which potentiated apoptosis induced by TNF and doxorubicin. Overall, our results indicate that SCH 66336 inhibited activation of NF-kappaB and NF-kappaB-regulated gene expressions induced by carcinogens and inflammatory stimuli, which may provide a molecular basis for the ability of SCH 66336 to suppress proliferation and angiogenesis.

L5 ANSWER 2 OF 45 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004092153 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14623898
TITLE: Down-regulation of the tumor suppressor PTEN by the tumor necrosis factor-alpha/nuclear factor-kappaB (NF-kappaB)-inducing kinase/NF-kappaB pathway is linked to a default IkappaB-alpha autoregulatory loop.
AUTHOR: Kim Sunghoon; Domon-Dell Claire; Kang Junghee; Chung Dai H; Freund Jean-Noel; Evers B Mark
CORPORATE SOURCE: Department of Surgery, The University of Texas Medical Branch, Galveston, Texas 77555-0536, USA.
CONTRACT NUMBER: P30-DK56338 (United States NIDDK) R01-DK35608 (United States NIDDK) R01-DK48498 (United States NIDDK) R37-AG10885 (United States NIA)
SOURCE: The Journal of biological chemistry, (2004 Feb 6) Vol. 279, No. 6, pp. 4285-91. Electronic Publication:

2003-11-17.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 2 Mar 2004
Last Updated on STN: 2 Apr 2004
Entered Medline: 1 Apr 2004

AB The PTEN (phosphatase and tensin homolog deleted on chromosome ten) tumor suppressor gene affects multiple cellular processes including cell growth, proliferation, and cell migration by antagonizing phosphatidylinositol 3-kinase (PI3K). However, mechanisms by which PTEN expression is regulated have not been studied extensively. Similar to PTEN, tumor necrosis factor-alpha (TNF-alpha) affects a wide spectrum of diseases including inflammatory processes and cancer by acting as a mediator of apoptosis, inflammation, and immunity. In this study, we show that treatment of cancer cell lines with TNF-alpha decreases PTEN expression. In addition, overexpression of TNF-alpha downstream signaling targets, nuclear factor-kappaB (NF-kappaB)-inducing kinase (NIK) and p65 nuclear factor NF-kappaB, lowers PTEN expression, suggesting that TNF-alpha-induced down-regulation of PTEN is mediated through a TNF-alpha/NIK/NF-kappaB pathway. Down-regulation of PTEN by NIK/NF-kappaB results in activation of the PI3K/Akt pathway and augmentation of TNF-alpha-induced PI3K/Akt stimulation. Importantly, we demonstrate that this effect is associated with a lack of an inhibitor of kappaB (IkappaB)-alpha autoregulatory loop. Moreover, these findings suggest the interaction between PI3K/Akt and NF-kappaB via transcriptional regulation of PTEN and offer one possible explanation for increased tumorigenesis in systems in which NF-kappaB is chronically activated. In such a tumor system, these findings suggest a positive feedback loop whereby Akt activation of NF-kappaB further stimulates Akt via down-regulation of the PI3K inhibitor PTEN.

L5 ANSWER 3 OF 45 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004310978 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15212763
TITLE: NF-kappaB inducing kinase activates NF-kappaB transcriptional activity independently of IkappaB kinase gamma through a p38 MAPK-dependent RelA phosphorylation pathway.
AUTHOR: Jijon H; Allard B; Jobin C
CORPORATE SOURCE: Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, CB 7032, 7341B Medical Biomolecular Research Building, Chapel Hill, NC 27599-7080, USA.
CONTRACT NUMBER: DK 47700 (United States NIDDK)
SOURCE: Cellular signalling, (2004 Sep) Vol. 16, No. 9, pp. 1023-32.
Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 25 Jun 2004

Last Updated on STN: 8 Jan 2005
Entered Medline: 7 Jan 2005

AB Molecular and biochemical analysis indicates that nuclear transcription factor kappaB (NF-kappaB)-inducing kinase (NIK) mediates IKK activation and NF-kappaB transcriptional activity. However, gene deletion studies suggest that NIK triggers gene expression without affecting IkappaBalpha degradation and NF-kappaB DNA binding activity. In order to investigate the role of NIK in NF-kappaB transcriptional activity, we used mouse embryonic fibroblasts (MEF) derived from wild-type (wt) and IkappaB kinase gamma (IKKgamma) gene deficient (IKKgamma(-/-)) mice. We report that although TNF-induced NF-kappaB transcriptional activity is abolished in IKKgamma(-/-) cells, adenoviral gene delivery of NIK (Ad5NIK) still enhanced transcriptional activity and IL-6 mRNA accumulation. Moreover, NIK targets the transactivation function of NF-kappaB through stimulation of the transactivation domain (TAD) of RelA (S536) in IKKgamma(-/-) cells. Interestingly, Ad5NIK, but not TNF, induces RelA S536 and p38 mitogen-activated protein kinase (MAPK) phosphorylation in IKKgamma(-/-) cells. Functional analysis demonstrated that Ad5NIK-induced NF-kappaB transcriptional activity, IL-6 mRNA expression and RelA phosphorylation are inhibited by the p38 inhibitor SB203580, suggesting a role for this MAPK in NIK signaling to NF-kappaB. These data demonstrate for the first time the presence of an IKKgamma-independent NIK/p38 MAPK-dependent signaling pathway that activates NF-kappaB and induces pro-inflammatory gene expression through RelA phosphorylation.

L5 ANSWER 4 OF 45 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2004309723 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14742314
TITLE: An acyclic retinoid, NIK-333, inhibits N-diethylnitrosamine-induced rat hepatocarcinogenesis through suppression of TGF-alpha expression and cell proliferation.
AUTHOR: Kagawa Masataka; Sano Tetsuro; Ishibashi Naoto; Hashimoto Manabu; Okuno Masataka; Moriwaki Hisataka; Suzuki Rikako; Kohno Hiroyuki; Tanaka Takuji
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Nikken Chemicals Co. Ltd, 1-346 Kitabukuro-cho, Omiya-ku, Saitama-shi, Saitama 330-0835, Japan.
SOURCE: Carcinogenesis, (2004 Jun) Vol. 25, No. 6, pp. 979-85. Electronic Publication: 2004-01-23.
Journal code: 8008055. ISSN: 0143-3334.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 25 Jun 2004
Last Updated on STN: 16 Jul 2004
Entered Medline: 15 Jul 2004

AB The present study was designed to determine the effects of NIK-333, a synthetic acyclic retinoid, on N-diethylnitrosamine (DEN)-induced hepatocarcinogenesis in male F344 rats. Animals were given DEN dissolved in drinking water at a concentration of 40 p.p.m. for 5 weeks and then provided with drinking water free of DEN for 15 weeks to induce hepatocellular neoplasms. NIK-333 was administered orally (once a day) to rats at doses of 10, 40 and 80 mg/kg body wt for 14 weeks, starting 1 week after the completion of administration of DEN. At 20 weeks after the start of DEN administration, histopathological evaluation was carried out on all animals. The effects of NIK-333 on the cell proliferation activity of non-tumorous areas and liver tumor cells and the immunohistochemical

expression of transforming growth factor-alpha (TGF-alpha) were also evaluated. NIK-333 at 40 and 80 mg/kg body wt significantly inhibited hepatocarcinogenesis ($P < 0.05$). In addition, NIK-333 at the same doses decreased DEN-induced overexpression of TGF-alpha in hepatocellular neoplasms (adenomas and carcinomas) and their surrounding tissue. Furthermore, NIK-333 significantly inhibited cell proliferation activity in the lesions and in non-tumorous areas ($P < 0.01$). Our results suggest that NIK-333 inhibits DEN-induced hepatocarcinogenesis through suppression of TGF-alpha expression and cell proliferation.

L5 ANSWER 5 OF 45 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2004449137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15356994
TITLE: Suppression of protein kinase C and nuclear oncogene expression as possible action mechanisms of cancer chemoprevention by Curcumin.
AUTHOR: Lin Jen-Kun
CORPORATE SOURCE: Institutes of Biochemistry, College of Medicine, National Taiwan University, No.1, Section 1, Jen-ai Road, Taipei, Taiwan, 10018.. jklin@ha.mc.ntu.edu.tw
SOURCE: Archives of pharmacal research, (2004 Jul) Vol. 27, No. 7, pp. 683-92. Ref: 63
Journal code: 8000036. ISSN: 0253-6269.
PUB. COUNTRY: Korea (South)
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 11 Sep 2004
Last Updated on STN: 19 Feb 2005
Entered Medline: 18 Feb 2005

AB Curcumin (diferuloylmethane) is a major naturally-occurring polyphenol of Curcuma species, which is commonly used as a yellow coloring and flavoring agent in foods. Curcumin has shown anti-carcinogenic activity in animal models. Curcumin possesses anti-inflammatory activity and is a potent inhibitor of reactive oxygen-generating enzymes such as lipoxygenase/cyclooxygenase, xanthine dehydrogenase/oxidase and inducible nitric oxide synthase; and an effective inducer of heme oxygenase-1. Curcumin is also a potent inhibitor of protein kinase C (PKC), EGF(Epidermal growth factor)-receptor tyrosine kinase and IkappaB kinase. Subsequently, curcumin inhibits the activation of NF(nucleor factor)kappaB and the expressions of oncogenes including c-jun, c-fos, c-myc, NIK, MAPKs, ERK, ELK, PI3K, Akt, CDKs and iNOS. It is proposed that curcumin may suppress tumor promotion through blocking signal transduction pathways in the target cells. The oxidant tumor promoter TPA activates PKC by reacting with zinc thiolates present within the regulatory domain, while the oxidized form of cancer chemopreventive agent such as curcumin can inactivate PKC by oxidizing the vicinal thiols present within the catalytic domain. Recent studies indicated that proteasome-mediated degradation of cell proteins play a pivotal role in the regulation of several basic cellular processes including differentiation, proliferation, cell cycling, and apoptosis. It has been demonstrated that curcumin-induced apoptosis is mediated through the impairment of ubiquitin-proteasome pathway. Curcumin was first biotransformed to dihydrocurcumin and tetrahydrocurcumin and that these compounds subsequently were converted to monoglucuronide conjugates. These results suggest that curcumin-glucuronide, dihydrocurcumin-glucuronide, tetrahydrocurcumin-glucuronide and tetrahydrocurcumin are the major metabolites of curcumin in mice, rats and humans.

L5 ANSWER 6 OF 45 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2004556833 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15528996
TITLE: IKKgamma inhibits activation of NF-kappaB by NIK.
AUTHOR: Kwon Woo Jong; Kim Sun Hee; Park Yeo Ok; Cho Mong; Kang Chi Dug; Lee Gwang; An Woo Gun; Joo Woo Hong; Kim Dong Wan
CORPORATE SOURCE: Department of Microbiology, College of Natural Sciences, Changwon National University, Changwon 641-773, Korea.
SOURCE: Molecules and cells, (2004 Oct 31) Vol. 18, No. 2, pp. 200-6.
Journal code: 9610936. ISSN: 1016-8478.
PUB. COUNTRY: Korea (South)
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 6 Nov 2004
Last Updated on STN: 6 Apr 2005
Entered Medline: 5 Apr 2005

AB IKKgamma is a component of the IKK complex, which regulates NF-kappaB activity. To investigate the role of IKKgamma, we expressed wild type IKKgamma containing 412 amino acids, and deletion mutants containing residues 1-312 and 101-412, using murine IKKgamma cDNA. In a co-transfection assay with a CAT reporter plasmid, NIK activated NF-kappaB-dependent gene expression approximately two fold and this expression was inhibited by co-transfection of a wild type IKKgamma expression plasmid. In binding assays IKKgamma inhibited the association of IkappaBalpha with IKKbeta and the subsequent phosphorylation of IkappaBalpha that is activated by NIK. Inhibition by IKKgamma also occurred in an assay with a dominant negative mutant of NIK but not with a C-terminal deletion mutant of IKKgamma, indicating that the C-terminal 100 amino acids of IKKgamma are important for negative regulation of NF-kappaB activation. In addition, the interaction of IKKbeta with IKKgamma was inhibited by co-transfection with a NIK expression plasmid. Our results suggest that overexpression of IKKgamma inhibits activation of NF-kappaB by NIK by competing with NIK for interaction with IKKbeta.

L5 ANSWER 7 OF 45 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2003313883 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12729461
TITLE: Fractalkine (CX3CL1) stimulated by nuclear factor kappaB (NF-kappaB)-dependent inflammatory signals induces aortic smooth muscle cell proliferation through an autocrine pathway.
AUTHOR: Chandrasekar Bysani; Mummidi Srinivas; Perla Rao P; Bysani Sailaja; Dulin Nickolai O; Liu Feng; Melby Peter C
CORPORATE SOURCE: Department of Medicine, University of Texas Health Science Center, San Antonio, TX 78229, USA..
chandraseka@uthscsa.edu
CONTRACT NUMBER: HL68020 (United States NHLBI)
SOURCE: The Biochemical journal, (2003 Jul 15) Vol. 373, No. Pt 2, pp. 547-58.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 8 Jul 2003
Last Updated on STN: 16 Aug 2003
Entered Medline: 15 Aug 2003

AB Fractalkine (also known as CX3CL1), a CX3C chemokine, activates and attracts monocytes/macrophages to the site of injury/inflammation. It binds to CX3C receptor 1 (CX3CR1), a pertussis toxin-sensitive G-protein-coupled receptor. In smooth muscle cells (SMCs), fractalkine is induced by proinflammatory cytokines [tumour necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma)], which may mediate monocyte adhesion to SMCs. However, the mechanisms underlying its induction are unknown. In addition, it is unlear whether SMCs express CX3CR1. TNF-alpha activated nuclear factor kappaB (NF-kappaB) and induced fractalkine and CX3CR1 expression in a time-dependent manner in rat aortic SMCs. Transient transfections with dominant-negative (dn) inhibitory kappaB (IkappaB)-alpha, dnIkappaB-beta, dnIkappaB kinase (IKK)-gamma, kinase-dead (kd) NF-kappaB-inducing kinase ( NIK) and kdIKK-beta, or pretreatment with wortmannin, Akt inhibitor, pyrrolidinecarbodithioc acid ammonium salt ('PDTC') or MG-132, significantly attenuated TNF-alpha-induced fractalkine and CX3CR1 expression. Furthermore, expression of dn TNF-alpha-receptor-associated factor 2 (TRAF2), but not dnTRAF6, inhibited TNF-alpha signal transduction. Pretreatment with pertussis toxin or neutralizing anti-CX3CR1 antibodies attenuated TNF-alpha-induced fractalkine expression, indicating that fractalkine autoregulation plays a role in TNF-alpha-induced sustained fractalkine expression. Fractalkine induced its own expression, via pertussis toxin-sensitive G-proteins, phosphoinositide 3-kinase (PI 3-kinase), phosphoinositide-dependent kinase 1 (PDK1), Akt, NIK, IKK and NF-kappaB activation, and induced SMC cell-cell adhesion and cellular proliferation. Taken together, our results demonstrate that TNF-alpha induces the expression of fractalkine and CX3CR1 in rat aortic SMCs and that this induction is mediated by NF-kappaB activation. We also show that fractalkine induces its own expression, which is mediated by the PI 3-kinase/PDK1/Akt/NIK/IKK/NF-kappaB signalling pathway. More importantly, fractalkine increased cell-cell adhesion and aortic SMC proliferation, indicating a role in initiation and progression of atherosclerotic vascular disease.

L5 ANSWER 8 OF 45 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2003125422 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12639713
TITLE: Induction of cyclooxygenase-2 by lipopolysaccharide in canine tracheal smooth muscle cells: involvement of p42/p44 and p38 mitogen-activated protein kinases and nuclear factor-kappaB pathways.
AUTHOR: Luo Shue-Fen; Wang Chuan-Chwan; Chien Chin-Sung; Hsiao Li-Der; Yang Chuen-Mao
CORPORATE SOURCE: Department of Internal Medicine, College of Medicine, Chang Gung University, Kwei-San, Tao-Yuan, Taiwan.
SOURCE: Cellular signalling, (2003 May) Vol. 15, No. 5, pp. 497-509.
Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 18 Mar 2003
Last Updated on STN: 15 Oct 2003
Entered Medline: 14 Oct 2003

AB Lipopolysaccharide (LPS) was found to induce inflammatory responses in the

airways and exerted as a potent stimulus for PG synthesis. This study was to determine the mechanisms of LPS-enhanced cyclooxygenase (COX)-2 expression associated with PGE(2) synthesis in tracheal smooth muscle cells (TSMCs). LPS markedly increased the expression of COX-2 and release of PGE(2) in a time- and concentration-dependent manner, whereas COX-1 remained unaltered. Both the expression of COX-2 and the generation of PGE(2) in response to LPS were attenuated by a tyrosine kinase inhibitor genistein, a phosphatidylcholine-phospholipase C inhibitor D609, a phosphatidylinositol-phospholipase C inhibitor U73122, protein kinase C inhibitors, GF109203X and staurosporine, removal of Ca(2+) by addition of BAPTA/AM plus EGTA, and phosphatidylinositol 3-kinase (PI3-K) inhibitors, LY294002 and wortmannin. Furthermore, LPS-induced NF-kappaB activation correlated with the degradation of IkappaB-alpha, COX-2 expression , and PGE(2) synthesis, was inhibited by transfection with dominant negative mutants of NIK and IKK-alpha, but not by IKK-beta. LPS-induced COX-2 expression and PGE(2) synthesis were completely inhibited by PD98059 (an inhibitor of MEK1/2) and SB203580 (an inhibitor of p38 MAPK inhibitor), but these two inhibitors had no effect on LPS-induced NF-kappaB activation, indicating that NF-kappaB is activated by LPS independently of activation of p42/p44 MAPK and p38 MAPK pathways in TSMCs. Taken together, these findings suggest that the increased expression of COX-2 correlates with the release of PGE(2) from LPS-challenged TSMCs, at least in part, independently mediated through MAPKs and NF-kappaB signalling pathways. LPS-mediated responses were modulated by PLC, Ca(2+), PKC, tyrosine kinase, and PI3-K in these cells.

L5 ANSWER 9 OF 45 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2003354061 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12716652
TITLE: Stretch-induced IL-8 depends on c-Jun NH2-terminal and nuclear factor-kappaB-inducing kinases.
AUTHOR: Li Li-Fu; Ouyang Bin; Choukroun Gabriel; Matyal Robina; Mascarenhas Marcella; Jafari Behrouz; Bonventre Joseph V; Force Thomas; Quinn Deborah A
CORPORATE SOURCE: Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.
CONTRACT NUMBER: HL-039020 (United States NHLBI)
HL-61688 (United States NHLBI)
HL-67371 (United States NHLBI)
SOURCE: American journal of physiology. Lung cellular and molecular physiology, (2003 Aug) Vol. 285, No. 2, pp. L464-75. Electronic Publication: 2003-04-25.
Journal code: 100901229. ISSN: 1040-0605.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 31 Jul 2003
Last Updated on STN: 1 Oct 2003
Entered Medline: 30 Sep 2003

AB Positive pressure ventilation with large tidal volumes has been shown to cause release of cytokines, including interleukin (IL)-8. The mechanisms regulating lung stretch-induced cytokine production are unclear. We hypothesized that stretch-induced IL-8 production is dependent on the activation of the mitogen-activated protein kinases, c-Jun NH2-terminal kinases (JNK), p38, and/or extracellular signal-regulated kinase (ERK) 1/2. We exposed A549 cells, a type II-like alveolar epithelial cell line, to cyclic stretch at 20 cycles/min for 5 min-2 h. Cyclic stretch induced IL-8 protein production, IL-8 mRNA expression, and JNK activation, but

only transient activation of p38 and ERK1/2. Inhibition of stretch-induced JNK activation by adenovirus-mediated gene transfer of stress-activated protein kinase (SEK-1), a dominant-negative mutant of SEK-1, the immediate upstream activator of the JNKs, and pharmacological JNK inhibitor II SP-600125 blocked IL-8 mRNA expression and attenuated IL-8 production. Inhibition of p38 and ERK1/2 did not affect stretch-induced IL-8 production. Stretch-induced activation NF-kappaB and activator protein (AP)-1 was blocked by NF-kappaB inhibitor and JNK inhibitor, respectively. An NF-IL-6 site was not essential for cyclic stretch-induced IL-8 promoter activity. Stretch also induced NF-kappaB-inducing kinase (NIK) activation, and inhibition of NF-kappaB attenuated IL-8 mRNA expression and IL-8 production. We conclude that stretch-induced transcriptional regulation of IL-8 mRNA and IL-8 production was via activation of AP-1 and NF-kappaB and was dependent on JNK and NIK activation, respectively.

L5 ANSWER 10 OF 45 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2002342279 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12085227
TITLE: Constitutive activation of NF-kappaB in Ki-ras-transformed prostate epithelial cells.
AUTHOR: Kim Bo-Yeon; Gaynor Richard B; Song Kyung; Dritschilo Anatoly; Jung Mira
CORPORATE SOURCE: Department of Radiation Medicine, Georgetown University School of Medicine, Washington DC 20007, USA.
CONTRACT NUMBER: CA45408 (United States NCI)
CA74175 (United States NCI)
SOURCE: Oncogene, (2002 Jul 4) Vol. 21, No. 29, pp. 4490-7.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 27 Jun 2002
Last Updated on STN: 19 Sep 2002
Entered Medline: 19 Jul 2002

AB The signaling pathway responsible for the activation of nuclear factor-kappaB (NF-kappaB) by oncogenic forms of Ras remains unclear. Both, the transactivation and DNA binding activities of NF-kappaB, were increased in 267B1 human prostate epithelial cells transformed by viral Kirsten-ras (267B1/Ki-ras cells) compared with those in the parental cells. This increased NF-kappaB activity was attributed to a heterodimeric complex of p50 and p65 subunits. Although the abundance of the inhibitor protein IkappaBbeta was higher in 267B1/Ki-ras cells than in 267B1 cells, an electrophoretic mobility-shift assay suggested that IkappaBalpha is responsible for the activation of NF-kappaB in the former cells. Consistent with this notion, the phosphorylation of IkappaBalpha appeared increased in 267B1/Ki-ras cells, and the proteasome inhibitor I abolished the constitutive activation of NF-kappaB in these cells. The expression of dominant negative mutants of either NIK (NF-kappaB-inducing kinase) or IKKbeta (IkappaB kinase beta) inhibited the activity of NF-kappaB in 267B1/Ki-ras cells. Furthermore, chemical inhibitors specific for Ras activation, sulindac sulfide and farnesytranferase inhibitor I, markedly reduced IkappaBalpha phosphorylation and NF-kappaB activation in the Ki-ras-transformed cells while transfection of these cells with NIK or IKKbeta counteracted the inhibitory effect on NF-kappaB activation. These results suggest that oncogenic Ki-Ras induces transactivation of NF-kappaB through the NIK-IKKbeta-IkappaBalpha pathway.

L5 ANSWER 11 OF 45 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 2002461760 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12220616
TITLE: Interleukin-1beta-induced cyclooxygenase-2 expression is mediated through activation of p42/44 and p38 MAPKS, and NF-kappaB pathways in canine tracheal smooth muscle cells.
AUTHOR: Yang Chuen-Mao; Chien Chin-Sung; Hsiao Li-Der; Luo Shu-Fen; Wang Chuan-Chwan
CORPORATE SOURCE: Department of Physiology and Pharmacology, College of Medicine, Chang Gung University, Kwei-San, Tao-Yuan, Taiwan.. chuenmao@mail.cgu.edu.tw
SOURCE: Cellular signalling, (2002 Nov) Vol. 14, No. 11, pp. 899-911.
Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 19 Apr 2003
Entered Medline: 18 Apr 2003

AB Interleukin-beta (IL-1beta) was found to induce inflammatory responses in the airways, which exerted a potent stimulus for PG synthesis. This study was to determine the mechanisms of IL-1beta-enhanced cyclooxygenase (COX)-2 expression associated with PGE(2) synthesis in tracheal smooth muscle cells (TSMCs). IL-1beta markedly increased COX-2 expression and PGE(2) formation in a time- and concentration-dependent manner in TSMCs. Both COX-2 expression and PGE(2) formation in response to IL-1beta were attenuated by a tyrosine kinase inhibitor, genistein, a phosphatidylcholine-phospholipase C inhibitor, D609, a phosphatidylinositol-phospholipase C inhibitor, U73122, protein kinase C inhibitors, GF109203X and staurosporine, removal of Ca(2+) by addition of BAPTA/AM plus EGTA, and phosphatidylinositol 3-kinase (PI3-K) inhibitors, LY294002 and wortmannin. IL-1beta-induced activation of NF-kappaB correlated with the degradation of IkappaB-alpha in TSMCs. IL-1beta-induced NF-kappaB activation, COX-2 expression, and PGE(2) synthesis were inhibited by the dominant negative mutants of NIK and IKK-alpha, but not by IKK-beta. IL-1beta-induced COX-2 expression and PGE(2) synthesis were completely inhibited by PD98059 (an inhibitor of MEK1/2) and SB203580 (an inhibitor of p38 inhibitor), but these two inhibitors had no effect on IL-1beta-induced NF-kappaB activation, indicating that activation of p42/44 and p38 MAPK and NF-kappaB signalling pathways were independently required for these responses. These findings suggest that the increased expression of COX-2 correlates with the release of PGE(2) from IL-1beta-challenged TSMCs, at least in part, independently mediated through MAPKs and NF-kappaB signalling pathways in canine TSMCs. IL-1beta-mediated responses were modulated by PLC, Ca(2+), PKC, tyrosine kinase, and PI3-K in these cells.

L5 ANSWER 12 OF 45 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 2002312589 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12055104
TITLE: Differential requirement for NF-kappaB-inducing kinase in the induction of NF-kappaB by IL-1beta, TNF-alpha, and Fas.
AUTHOR: Russo Maria P; Bennett Brydon L; Manning Anthony M; Brenner David A; Jobin Christian
CORPORATE SOURCE: Department of Medicine and Center for Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill, North Carolina 27599-7080, USA.

CONTRACT NUMBER: R01-DK47700 (United States NIDDK)
SOURCE: American journal of physiology. Cell physiology, (2002 Jul) Vol. 283, No. 1, pp. C347-57.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 11 Jun 2002
Last Updated on STN: 17 Jul 2002
Entered Medline: 16 Jul 2002

AB In this study, we examined the role of the nuclear factor-kappaB (NF-kappaB)-inducing kinase (NIK) in distinct signaling pathways leading to NF-kappaB activation. We show that a dominant-negative form of NIK (dnNIK) delivered by adenoviral (Ad5dnNIK) vector inhibits Fas-induced IkappaBalpha phosphorylation and NF-kappaB-dependent gene expression in HT-29 and HeLa cells. Interleukin (IL)-1beta- and tumor necrosis factor-alpha (TNF-alpha)-induced NF-kappaB activation and kappaB-dependent gene expression are inhibited in HeLa cells but not in Ad5dnNIK-infected HT-29 cells. Moreover, Ad5dnNIK failed to sensitize HT-29 cells to TNF-alpha-induced apoptosis at an early time point. However, cytokine- and Fas-induced signals to NF-kappaB are finally integrated by the IkappaB kinase (IKK) complex, since IkappaBalpha phosphorylation, NF-kappaB DNA binding activity, and IL-8 gene expression were strongly inhibited in HT-29 and HeLa cells overexpressing dominant-negative IKKbeta (Ad5dnIKKbeta). Our findings support the concept that cytokine signaling to NF-kappaB is redundant at the level of NIK. In addition, this study demonstrates for the first time the critical role of NIK and IKKbeta in Fas-induced NF-kappaB signaling cascade.

L5 ANSWER 13 OF 45 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2001291007 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11278990
TITLE: Inhibition of the nuclear factor kappa B (NF-kappa B) pathway by tetracyclic kaurene diterpenes in macrophages. Specific effects on NF-kappa B-inducing kinase activity and on the coordinate activation of ERK and p38 MAPK.
AUTHOR: Castrillo A; de Las Heras B; Hortelano S; Rodriguez B; Villar A; Bosca L
CORPORATE SOURCE: Instituto de Bioquimica, Centro Mixto Consejo Superior de Investigaciones Cientificas-Universidad Complutense de Madrid, Spain.
SOURCE: The Journal of biological chemistry, (2001 May 11) Vol. 276, No. 19, pp. 15854-60. Electronic Publication: 2001-02-09.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 18 Jun 2001
Last Updated on STN: 5 Jan 2003
Entered Medline: 14 Jun 2001

AB The anti-inflammatory action of most terpenes has been explained in terms of the inhibition of nuclear factor kappaB (NF-kappaB) activity. Ent-kaurene diterpenes are intermediates of the synthesis of gibberellins and inhibit the expression of NO synthase-2 and the release of tumor

necrosis factor-alpha in J774 macrophages challenged with lipopolysaccharide. These diterpenes inhibit NF-kappaB and IkappaB kinase (IKK) activation in vivo but failed to affect in vitro the function of NF-kappaB, the phosphorylation and targeting of IkappaBalpha, and the activity of IKK-2. Transient expression of NF-kappaB-inducing kinase (NIK) activated the IKK complex and NF-kappaB, a process that was inhibited by kaurenes, indicating that the inhibition of NIK was one of the targets of these diterpenes. These results show that kaurenes impair the inflammatory signaling by inhibiting NIK, a member of the MAPK kinase superfamily that interacts with tumor necrosis factor receptor-associated factors, and mediate the activation of NF-kappaB by these receptors. Moreover, kaurenes delayed the phosphorylation of p38, ERK1, and ERK2 MAPKs, but not that of JNK, in response to lipopolysaccharide treatment of J774 cells. The absence of a coordinate activation of MAPK and IKK might contribute to a deficient activation of NF-kappaB that is involved in the anti-inflammatory activity of these molecules.

L5 ANSWER 14 OF 45 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 2001208143 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11254583
TITLE: Micrococci and peptidoglycan activate TLR2-->MyD88-->IRAK-->TRAF-->NIK-->IKK-->NF-kappaB signal transduction pathway that induces transcription of interleukin-8.
AUTHOR: Wang Q; Dziarski R; Kirschning C J; Muzio M; Gupta D
CORPORATE SOURCE: Northwest Center for Medical Education, Indiana University School of Medicine, Gary, Indiana 46408, USA.
CONTRACT NUMBER: AI28797 (United States NIAID)
SOURCE: Infection and immunity, (2001 Apr) Vol. 69, No. 4, pp. 2270-6.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 17 Apr 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 12 Apr 2001
AB This study was done to elucidate the signal transduction pathway of interleukin-8 (IL-8) induction by gram-positive bacteria. Bacteria (micrococci) and peptidoglycan (PGN) induced transcription of IL-8 in HEK293 cells expressing Toll-like receptor 2 (TLR2) and CD14 but not in those expressing TLR1 or TLR4. A mutation within the NF-kappaB site in the IL-8 promoter abrogated transcriptional induction of IL-8 by the two stimulants. Dominant negative myeloid differentiation protein (MyD88), IL-1 receptor-associated kinase (IRAK), NFkappaB-inducing kinase ( NIK), and IkappaB kinase (IKK) mutant forms completely inhibited micrococcus- and PGN-induced activation of NF-kappaB and expression of the gene for IL-8. Induction of NF-kappaB was partially inhibited by dominant negative tumor necrosis factor receptor-associated kinase 6 (TRAF6) but not TRAF2, whereas induction of IL-8 gene was partially inhibited by both TRAF6 and TRAF2. These data indicate that micrococci and PGN induce TLR2-dependent activation of the gene for IL-8 and that this activation requires MyD88, IRAK, NIK, IKK, and NF-kappaB and may also utilize TRAF6 and, to a lesser extent, TRAF2.

L5 ANSWER 15 OF 45 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 2001466101 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11510478
TITLE: Modulation of gene expression by (-)-epigallocatechin

gallate in PC-9 cells using a cDNA expression array.
AUTHOR: Okabe S; Fujimoto N; Sueoka N; Suganuma M; Fujiki H
CORPORATE SOURCE: Saitama Cancer Center, Japan.
SOURCE: Biological & pharmaceutical bulletin, (2001 Aug) Vol. 24, No. 8, pp. 883-6.
Journal code: 9311984. ISSN: 0918-6158.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 21 Aug 2001
Last Updated on STN: 28 Jan 2002
Entered Medline: 23 Jan 2002

AB Green tea is the most effective cancer preventive beverage. In the light of this, the mechanisms of action of tea polyphenols were investigated on the molecular levels. We present here the effects of (-)-epigallocatechin gallate (EGCG) on expression of 588 genes in human lung cancer cell line PC-9 cells, using a human cancer cDNA expression array. The levels of gene expression in non-treated control cells, and cells treated with EGCG alone, with the tumor promoter okadaic acid alone, and with EGCG plus okadaic acid, were studied, and their expression levels were classified into down-regulation (under 0.5 fold) and up-regulation (over 2.0 fold) by comparing with the levels of control. Non-treated PC-9 cells expressed 163 genes out of 588, and EGCG-treated cells induced down-regulated expression of 12 genes and up-regulated expression of 4 other genes. From a comparison of gene expression in the cells treated with EGCG and in cells treated with EGCG plus okadaic acid, we found the following genes commonly affected by EGCG: down-regulation of four genes, NF-kappaB inducing kinase (NIK), death-associated protein kinase 1 (DAPK 1), rhoB and tyrosine-protein kinase (SKY); up-regulation of one gene, retinoic acid receptor alpha1. Among them, we think down-regulation of NIK gene expression is significant for cancer prevention, based on evidence that inhibition of NF-kappaB activation is a result of inhibition of NIK/IKK signalling complex.

L5 ANSWER 16 OF 45 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 2003402255 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12940066
TITLE: Effect of mm-LDL on NF-kB activation in endothelial cell.
AUTHOR: Yin H C; Liu X Y; Liu P M; Zhang H; Liang P; Wang Z L; She M P
CORPORATE SOURCE: Department of Pathology, Institute of Basic Medical Sciences, CAMS and PUMC, Beijing 100005, China.
SOURCE: Zhongguo yi xue ke xue yuan xue bao. Acta Academiae Medicinae Sinicae, (2001 Aug) Vol. 23, No. 4, pp. 312-6.
Journal code: 8006230. ISSN: 1000-503X.
PUB. COUNTRY: China
DOCUMENT TYPE: (COMPARATIVE STUDY)
(ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 28 Aug 2003
Last Updated on STN: 11 Jun 2004
Entered Medline: 10 Jun 2004

AB OBJECTIVE: To investigate the signal transduction pathway of NF-kB

activated by minimally modified low density lipoprotein (mm-LDL) in endothelial cells and the effect of NF-kB on platelet derived growth factor b (PDGFb) mRNA expression. METHODS: mm-LDL was prepared through iron oxidation by dialyzing the native LDL against FeSO4 in PBS. Endothelial cells were incubated in a medium containing mm-LDL, TNF, and IL-1 respectively and electrophoretic mobility shift assay (EMSA) was displayed to check on the activation of NF-kB. Luciferase reporter gene was analysed to investigate the effect of nuclear factor inducing kinase (NIK), inhibitor of NF-kB kinase alpha (IKK alpha) and inhibitor of NF-kB kinase beta (IKK beta) on NF-kB activation. In addition, endothelial cells were transfected using PDGFb promoter-luciferase for reporter gene analysis or transfected with mut-NIK for slot blot analysis to study the effect of NF-kB on PDGFb mRNA expression. RESULTS: mm-LDL was able to activate NF-kB in endothelial cells. mut-NIK and mut-IKK beta inhibited luciferase activity induced by mm-LDL. mm-LDL could also enhance luciferase activity controlled by upstream sequence of PDGFb promoter which contains element interacting with NF-kB. Result of slot blot showed inhibition of PDGFb mRNA expression by mut-NIK
in the endothelial cells stimulated by mm-LDL. CONCLUSION: mm-LDL may activate NF-kB through NIK-IKK beta pathway and promote PDGFb mRNA expression in endothelial cells.

L5 ANSWER 17 OF 45 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 2001112017 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11136824
TITLE: Modulation of the nuclear factor kappa B pathway by Shp-2 tyrosine phosphatase in mediating the induction of interleukin (IL)-6 by IL-1 or tumor necrosis factor.
AUTHOR: You M; Flick L M; Yu D; Feng G S
CORPORATE SOURCE: Burnham Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: CA78606 (United States NCI)
GM53660 (United States NIGMS)
SOURCE: The Journal of experimental medicine, (2001 Jan 1) Vol. 193, No. 1, pp. 101-10.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 8 Feb 2001

AB Shp-2, a src homology (SH)2-containing phosphotyrosine phosphatase, appears to be involved in cytoplasmic signaling downstream of a variety of cell surface receptors, although the mechanism is unclear. Here, we have determined a role of Shp-2 in the cytokine circuit for inflammatory and immune responses. Production of interleukin (IL)-6 in response to IL-1 alpha or tumor necrosis factor (TNF)-alpha was nearly abolished in homozygous mutant (Shp-2(-/)-) fibroblast cells. The targeted Shp-2 mutation has no significant effect on the activation of the three types of mitogen-activated protein (MAP) kinases, extracellular signal-regulated kinase (Erk), c-Jun NH(2)-terminal kinase (Jnk), and p38, by IL-1/TNF, indicating that Shp-2 does not work through MAP kinase pathways in mediating IL-1/TNF-induced IL-6 synthesis. In contrast, IL-1/TNF-stimulated nuclear factor (NF)-kappa B DNA binding activity and inhibitor of kappa B (I kappa B) phosphorylation was dramatically decreased in Shp-2(-/)- cells, while the expression and activity of NF-kappa B-inducing
kinase (NIK), Akt, and I kappa B kinase (IKK) were not changed. Reintroduction of a wild-type Shp-2 protein into Shp-2(-/)-

cells rescued NF-kappa B activation and IL-6 production in response to IL-1/TNF stimulation. Furthermore, Shp-2 tyrosine phosphatase was detected in complexes with IKK as well as with IL-1 receptor. Thus, this SH2-containing enzyme is an important cytoplasmic factor required for efficient NF-kappa B activation. These results elucidate a novel mechanism of Shp-2 in cytokine signaling by specifically modulating the NF-kappa B pathway in a MAP kinase-independent fashion.

L5 ANSWER 18 OF 45 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 2000115874 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10648614
TITLE: NF-kappaB activation by double-stranded-RNA-activated protein kinase (PKR) is mediated through NF-kappaB-inducing kinase and IkappaB kinase.
AUTHOR: Zamanian-Daryoush M; Mogensen T H; DiDonato J A; Williams B R
CORPORATE SOURCE: Department of Cancer Biology, The Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.
CONTRACT NUMBER: AI34039 (United States NIAID)
SOURCE: Molecular and cellular biology, (2000 Feb) Vol. 20, No. 4, pp. 1278-90.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 29 Feb 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 15 Feb 2000
AB The interferon (IFN)-inducible double-stranded-RNA (dsRNA)-activated serine-threonine protein kinase (PKR) is a major mediator of the antiviral and antiproliferative activities of IFNs. PKR has been implicated in different stress-induced signaling pathways including dsRNA signaling to nuclear factor kappa B (NF-kappaB). The mechanism by which PKR mediates activation of NF-kappaB is unknown. Here we show that in response to poly(rI). poly(rC) (pIC), PKR activates IkappaB kinase (IKK), leading to the degradation of the inhibitors IkappaBalpha and IkappaBbeta and the concomitant release of NF-kappaB. The results of kinetic studies revealed that pIC induced a slow and prolonged activation of IKK, which was preceded by PKR activation. In PKR null cell lines, pIC failed to stimulate IKK activity compared to cells from an isogenic background wild type for PKR in accord with the inability of PKR null cells to induce NF-kappaB in response to pIC. Moreover, PKR was required to establish a sustained response to tumor necrosis factor alpha (TNF-alpha) and to potentiate activation of NF-kappaB by cotreatment with TNF-alpha and IFN-gamma. By coimmunoprecipitation, PKR was shown to be physically associated with the IKK complex. Transient expression of a dominant negative mutant of IKKbeta or the NF-kappaB-inducing kinase ( NIK) inhibited pIC-induced gene expression from an NF-kappaB-dependent reporter construct. Taken together, these results demonstrate that PKR-dependent dsRNA induction of NF-kappaB is mediated by NIK and IKK activation.

L5 ANSWER 19 OF 45 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 1999329013 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10400625
TITLE: c-E10 is a caspase-recruiting domain-containing protein that interacts with components of death receptors signaling

pathway and activates nuclear factor-kappaB.
AUTHOR: Costanzo A; Guiet C; Vito P
CORPORATE SOURCE: Fondazione A. Cesalpino, I Clinica Medica, V.le Policlinico 155, 00161 Roma, Italy.
SOURCE: The Journal of biological chemistry, (1999 Jul 16) Vol. 274, No. 29, pp. 20127-32. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF105066
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 27 Aug 1999
Last Updated on STN: 27 Aug 1999
Entered Medline: 19 Aug 1999

AB Members of the tumor necrosis factor receptor superfamily induce apoptosis via interaction with FADD and regulate cell growth and differentiation through TRADD and TRAFs molecules. While screening for molecules involved in the regulation of death receptor signaling, we identified a novel protein, c-E10. c-E10 contains an amino-terminal caspase-recruiting domain (CARD) and shares a sequence homologous with E10, a viral CARD-containing protein that binds to c-E10. In transfection experiments c-E10 oligomerizes, binds to the cytoplasmic portion of TRAIL receptor 1 (DR4) and coprecipitates with TRADD. Expression of c-E10 under the control of a doxycycline-dependent transcriptional transactivator results in NF-kappaB activation, which is inhibited by dominant negative forms of TRAF2 and NIK kinase. Thus, our results suggest that c-E10 is an adapter protein that activates NF-kappaB through a molecular pathway involved in death receptor signaling.

L5 ANSWER 20 OF 45 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 1999321931 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10391945
TITLE: Differential IkappaB kinase activation and IkappaBalpha degradation by interleukin-1beta and tumor necrosis factor-alpha in human U937 monocytic cells. Evidence for additional regulatory steps in kappaB-dependent transcription.
AUTHOR: Nasuhara Y; Adcock I M; Catley M; Barnes P J; Newton R
CORPORATE SOURCE: Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London SW3 6LY, United Kingdom.
SOURCE: The Journal of biological chemistry, (1999 Jul 9) Vol. 274, No. 28, pp. 19965-72. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 16 Aug 1999
Last Updated on STN: 19 Sep 2002
Entered Medline: 5 Aug 1999

AB The IkappaB kinases (IKKs) lie downstream of the NF-kappaB-inducing kinase (NIK) and activate NF-kappaB by phosphorylation of IkappaBalpha. This leads to IkappaBalpha degradation and release of NF-kappaB. In U937 monocytic cells, interleukin (IL)-1beta (1 ng/ml) and tumor necrosis factor (TNF)-alpha; 10 ng/ml) induced kappaB-dependent transcription equally. However, IKK activity was strongly induced by TNF-alpha but not

by IL-1beta. This was consistent with IkappaBalpha phosphorylation and degradation, yet TNF-alpha-induced NF-kappaB DNA binding was only 30-40% greater than for IL-1beta. This was not explained by degradation of IkappaBbeta, IkappaBepsilon, or p105 nor nuclear translocation of NF-kappaB. IkappaBalpha complexes or degradation-independent release of NF-kappaB. Dominant negative (NIK) repressed TNF-alpha and IL-1beta-induced kappaB-dependent transcription by approximately 60% and approximately 35%, respectively. These data reveal an imprecise relationship between IKK activation, IkappaBalpha degradation, and NF-kappaB DNA binding, suggesting the existence of additional mechanisms that regulate NF-kappaB activation. Finally, the lack of correlation between DNA binding and transcriptional activation plus the fact that PP1 and genistein both inhibited kappaB-dependent transcription without affecting DNA binding activity demonstrate the existence of regulatory steps downstream of NF-kappaB DNA binding. Therapeutically these data are important as inhibition of the NIK-IKK-IkappaBalpha cascade may not produce equivalent reductions in NF-kappaB-dependent gene expression.

L5 ANSWER 21 OF 45 MEDLINE on STN DUPLICATE 26
ACCESSION NUMBER: 1999214545 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10187770
TITLE: CIPER, a novel NF kappaB-activating protein containing a caspase recruitment domain with homology to Herpesvirus-2 protein E10.
AUTHOR: Koseki T; Inohara N; Chen S; Carrio R; Merino J; Hottiger M O; Nabel G J; Nunez G
CORPORATE SOURCE: Department of Pathology and Comprehensive Cancer Center, The University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.
CONTRACT NUMBER: CA-64421 (United States NCI)
CA-64556 (United States NCI)
SOURCE: The Journal of biological chemistry, (1999 Apr 9) Vol. 274, No. 15, pp. 9955-61.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF057700; GENBANK-AF057701
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 17 May 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 3 May 1999
AB We have identified and characterized CIPER, a novel protein containing a caspase recruitment domain (CARD) in its N terminus and a C-terminal region rich in serine and threonine residues. The CARD of CIPER showed striking similarity to E10, a product of the equine herpesvirus-2. CIPER formed homodimers via its CARD and interacted with viral E10 but not with several apoptosis regulators containing CARDs including ARC, RAIDD, RICK, caspase-2, caspase-9, or Apaf-1. Expression of CIPER induced NF-kappaB activation, which was inhibited by dominant-negative NIK and a nonphosphorylable IkappaB-alpha mutant but not by dominant-negative RIP. Mutational analysis revealed that the N-terminal region of CIPER containing the CARD was sufficient and necessary for NF-kappaB-inducing activity. Point mutations in highly conserved residues in the CARD of CIPER disrupted the ability of CIPER to activate NF-kappaB and to form homodimers, indicating that the CARD is essential for NF-kappaB activation and dimerization. We propose that CIPER acts in a

NIK-dependent pathway of NF-kappaB activation.

L5 ANSWER 22 OF 45 MEDLINE on STN DUPLICATE 27
ACCESSION NUMBER: 2000027389 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10557090
TITLE: Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex.
AUTHOR: Plummer S M; Holloway K A; Manson M M; Munks R J; Kaptein A; Farrow S; Howells L
CORPORATE SOURCE: MRC Toxicology Unit, University of Leicester, Leicester, LE1 9HN, UK.
SOURCE: Oncogene, (1999 Oct 28) Vol. 18, No. 44, pp. 6013-20.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 13 Jan 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 3 Dec 1999

AB Colorectal cancer is a major cause of cancer deaths in Western countries, but epidemiological data suggest that dietary modification might reduce these by as much as 90%. Cyclo-oxygenase 2 (COX2), an inducible isoform of prostaglandin H synthase, which mediates prostaglandin synthesis during inflammation, and which is selectively overexpressed in colon tumours, is thought to play an important role in colon carcinogenesis. Curcumin, a constituent of turmeric, possesses potent anti-inflammatory activity and prevents colon cancer in animal models. However, its mechanism of action is not fully understood. We found that in human colon epithelial cells, curcumin inhibits COX2 induction by the colon tumour promoters, tumour necrosis factor alpha or fecapentaene-12. Induction of COX2 by inflammatory cytokines or hypoxia-induced oxidative stress can be mediated by nuclear factor kappa B (NF-kappaB). Since curcumin inhibits NF-kappaB activation, we examined whether its chemopreventive activity is related to modulation of the signalling pathway which regulates the stability of the NF-kappaB-sequestering protein, IkappaB. Recently components of this pathway, NF-kappaB-inducing kinase and IkappaB kinases, IKKalpha and beta, which phosphorylate IkappaB to release NF-kappaB, have been characterised. Curcumin prevents phosphorylation of IkappaB by inhibiting the activity of the IKKs. This property, together with a long history of consumption without adverse health effects, makes curcumin an important candidate for consideration in colon cancer prevention.

L5 ANSWER 23 OF 45 MEDLINE on STN DUPLICATE 28
ACCESSION NUMBER: 1999315915 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10385526
TITLE: The zinc finger protein A20 inhibits TNF-induced NF-kappaB-dependent gene expression by interfering with an RIP- or TRAF2-mediated transactivation signal and directly binds to a novel NF-kappaB-inhibiting protein ABIN.
AUTHOR: Heyninck K; De Valck D; Vanden Berghe W; Van Criekinge W; Contreras R; Fiers W; Haegeman G; Beyaert R
CORPORATE SOURCE: Department of Molecular Biology, Flanders Interuniversity Institute for Biotechnology, University of Ghent, B-9000 Ghent, Belgium.
SOURCE: The Journal of cell biology, (1999 Jun 28) Vol. 145, No. 7, pp. 1471-82.

Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
OTHER SOURCE: GENBANK-AJ242777; GENBANK-AJ242778
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 16 Aug 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 2 Aug 1999

AB The zinc finger protein A20 is a tumor necrosis factor (TNF)- and interleukin 1 (IL-1)-inducible protein that negatively regulates nuclear factor-kappa B (NF-kappaB)-dependent gene expression. However, the molecular mechanism by which A20 exerts this effect is still unclear. We show that A20 does not inhibit TNF- induced nuclear translocation and DNA binding of NF-kappaB, although it completely prevents the TNF- induced activation of an NF-kappaB-dependent reporter gene, as well as TNF-induced IL-6 and granulocyte macrophage-colony stimulating factor gene expression. Moreover, NF-kappaB activation induced by overexpression of the TNF receptor-associated proteins TNF receptor-associated death domain protein (TRADD), receptor interacting protein (RIP), and TNF recep- tor-associated factor 2 (TRAF2) was also inhibited by expression of A20, whereas NF-kappaB activation induced by overexpression of NF-kappaB-inducing kinase (NIK) or the human T cell leukemia virus type 1 (HTLV-1) Tax was unaffected. These results demonstrate that A20 inhibits NF-kappaB-dependent gene expression by interfering with a novel TNF-induced and RIP- or TRAF2-mediated pathway that is different from the NIK-IkappaB kinase pathway and that is specifically involved in the transactivation of NF-kappaB. Via yeast two-hybrid screening, we found that A20 binds to a novel protein, ABIN, which mimics the NF-kappaB inhibiting effects of A20 upon overexpression, suggesting that the effect of A20 is mediated by its interaction with this NF-kappaB inhibiting protein, ABIN.

L5 ANSWER 24 OF 45 MEDLINE on STN DUPLICATE 29
ACCESSION NUMBER: 1999098989 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9882303
TITLE: Epstein-Barr virus-encoded latent membrane protein 1 activates the JNK pathway through its extreme C terminus via a mechanism involving TRADD and TRAF2.
AUTHOR: Eliopoulos A G; Blake S M; Floettmann J E; Rowe M; Young L S
CORPORATE SOURCE: CRC Institute for Cancer Studies, The University of Birmingham Medical School, Birmingham B15 2TA, England.
SOURCE: Journal of virology, (1999 Feb) Vol. 73, No. 2, pp. 1023-35.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 1 Mar 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 18 Feb 1999

AB The transforming Epstein-Barr virus-encoded latent membrane protein 1 (LMP1) activates signalling on the NF-kappaB axis through two distinct domains in its cytoplasmic C terminus, namely, CTAR1 (amino acids [aa] 187 to 231) and CTAR2 (aa 351 to 386). The ability of CTAR1 to activate NF-kappaB appears to be attributable to the direct interaction of tumor

necrosis factor (TNF) receptor-associated factor 2 (TRAF2), while recent work indicates that CTAR2-induced NF-kappaB is mediated through its association with TNF receptor-associated death domain (TRADD). LMP1 expression also results in activation of the c-Jun N-terminal kinase (JNK) (also known as stress-activated protein kinase) cascade, an effect which is mediated exclusively through CTAR2 and can be dissociated from NF-kappaB induction. The organization and signalling components involved in LMP1-induced JNK activation are not known. In this study we have dissected the extreme C terminus of LMP1 and have identified the last 8 aa of the protein (aa 378 to 386) as being important for JNK signalling. Using a series of fine mutants in which single amino acids between codons 379 and 386 were changed to glycine, we have found that mutations of Pro379, Glu381, Ser383, or Tyr384 diminish the ability of LMP1 CTAR2 to engage JNK signalling. Interestingly, this region was also found to be essential for CTAR2-mediated NF-kappaB induction and coincides with the LMP1 amino acid sequences shown to bind TRADD. Furthermore, we have found that LMP1-mediated JNK activation is synergistically augmented by low levels of TRADD expression, suggesting that this adapter protein is critical for LMP1 signalling. TRAF2 is known to associate with TRADD, and expression of a dominant-negative N-terminal deletion TRAF2 mutant was found to partially inhibit LMP1-induced JNK activation in 293 cells. In addition, the TRAF2-interacting protein A20 blocked both LMP1-induced JNK and NF-kappaB activation, further implicating TRAF2 in these phenomena. While expression of a kinase-inactive mutated NF-kappaB-inducing kinase (NIK), a mitogen-activated protein kinase kinase kinase which also associates with TRAF2, impaired LMP1 signalling on the NF-kappaB axis, it did not inhibit LMP1-induced JNK activation, suggesting that these two pathways may bifurcate at the level of TRAF2. These data further define a role for TRADD and TRAF2 in JNK activation and confirm that LMP1 utilizes signalling mechanisms used by the TNF receptor/CD40 family to elicit its pleiotropic activities.

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AT 17:39:34 ON 24 SEP 2008
FILE 'MEDLINE' ENTERED AT 17:39:34 ON 24 SEP 2008
FILE 'BIOSIS' ENTERED AT 17:39:34 ON 24 SEP 2008

FILE 'CAPLUS' ENTERED AT 17:39:34 ON 24 SEP 2008

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FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 17:16:47 ON 24 SEP 2008
L1 0 S SIRNA (S) NIK AND PD<=20041130
L2 17 S RNA (S) NIK AND PD<=20041130
L3 9 DUP REM L2 (8 DUPLICATES REMOVED)
L4 114 S EXPRESSION (S) (DOWN-REGULAT? OR INHIBIT?) (S) (NIK OR (NF-KA
L5 45 DUP REM L4 (69 DUPLICATES REMOVED)

=> D Ibib abs L5 25-45

L5 ANSWER 25 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:476356 BIOSIS
DOCUMENT NUMBER: PREV200510268260
TITLE: Rituximab-mediated inhibition of the constitutive NIK/IKK/I kappa B/NF-kappa B signaling pathway in non-Hodgkin's lymphoma (NHL) B-cell lines: Role in chemo-sensitization.
AUTHOR(S): Jazirehi, Ali R. [Reprint Author]; Huerta-Yepez, Sara; Cheng, Genhong; Bonavida, Benjamin
CORPORATE SOURCE: Univ Calif Los Angeles, Los Angeles, CA USA
SOURCE: Blood, (NOV 16 2004) Vol. 104, No. 11, Part 1, pp. 86A.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005
AB The chimeric anti-CD20 antibody rituximab (Rituxan, IDEC-C2B8) is widely used in the clinical treatment of patients with non-Hodgkin's lymphoma (NHL). Rituximab sensitizes NHL B-cell lines to drug-induced apoptosis via selective down-regulation of Bcl-(xL) expression (Jazirehi et al., Mol. Cancer Therapeutics 2:1183, 2003). We hypothesized that rituximab-mediated down-regulationof Bcl-(xL) expression may be due, in part, to inhibition of constitutive NF-kappa B activity that regulates Bcl-(XL) expression. This hypothesis was tested following treatment with rituximab of CD20+ drug-resistantRamos (Bcl-2(-)/ Bcl-(+)(xK)) and Daudi (Bcl-2(+)/ Bcl-(+)(xK)) cell lines. Rituximab decreased the phosphorylation of NIK, IKK and I kappa B-alpha, diminished IKK kinase activityand decreased NF-kappa B DNA-binding activity. These events and down-regulation of BCl-(xL) expression occurred with similar kinetics and were observed 3-6 h post rituximab treatment. The role of NF-kappa B in the regulationof Bcl-(xL) transcription in both Ramos and Daudi cells was demonstrated by using 1) promoter reporter assays in which deletion of the two tandem NF-kappa B binding sites in the upstream promoter region significantly reducedthe luciferase activity 2) I kappa B super-repressor expressing cells and 3) by NF-kappa B specific inhibitors. The underlying mechanism of the inhibition of the NF-kappa B signaling pathway by rituximab was shown to be due, in part,to upregulation of Raf-1 kinase inhibitor protein (RKIP) expression, thus, interrupting the NF-kappa B signaling pathway through the physical association between NIK and RKIP, which was concomitant with Bcl-(xL) down-

regulation. The direct role of Bcl-(xL) in drug-resistance was evaluated by using Bcl-(xL) over-expressing Ramos cells, which exhibited higher resistance to drugs that was partially reversed by rituximab. These findings reveal a novel mechanism of action of rituximab-mediated signaling by inducing RKIP expression that negatively regulates the constitutive NF-kappa B pathway resulting in Bcl-(xL) down-regulation and chemosensitization of the NHLB-cells. Furthermore. these findings identify several targets, namely RKIP, Bcl-(xL) and the components of the NF-kappa B signaling pathway, for therapeutic intervention in combination with cytotoxic agents to reverse adaptive. and acquired resistance of B-NHL.

L5 ANSWER 26 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:7452 BIOSIS
DOCUMENT NUMBER: PREV200400008383
TITLE: Inhibitor of the inflammatory response induced by TNFalpha and IL-1.
AUTHOR(S): Greene, Warner C. [Inventor, Reprint Author]; Lin, Xin [Inventor]; Gelezuinas, Romas [Inventor]
CORPORATE SOURCE: ASSIGNEE: The Regents of the University of California
PATENT INFORMATION: US 6645728 20031111
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov 11 2003) Vol. 1276, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Dec 2003
Last Updated on STN: 17 Dec 2003
AB The present invention provides the molecular basis for cytokine induction of NF-kappaB-dependent immune and inflammatory responses, emphasizing a role for both NIK-NIK and NIK-IKK protein--protein interactions. A relatively small region of NIK selectively impairs the NIK-IKK interaction. The present invention provides a novel and highly specific method for modulating NF-kappaB-dependent immune, inflammatory, and anti-apoptotic responses, based on interruption of the critical protein--protein interaction of NIK and IKK. The present invention provides methods for inhibiting NF-kappaB-dependent gene expression, using mutant NIK proteins. One embodiment of the present invention provides kinase-deficient NIK mutant proteins that inhibit activation of IKK. Another embodiment of the invention provides N-terminus NIK mutant proteins that bind IKK, thus inhibiting NIK/IKK interaction.

L5 ANSWER 27 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:582358 BIOSIS
DOCUMENT NUMBER: PREV200300572193
TITLE: PROTEIN KINASE C-DELTA PLAYS A PIVOTAL ROLE IN GASTRIN-INDUCED ACTIVATION OF NF-kappaB IN GASTRIC EPITHELIAL CELLS .
AUTHOR(S): Toyota, Miyuki [Reprint Author]; Miyazaki, Yoshiji [Reprint Author]; Kishida, Osamu [Reprint Author]; Miyazaki, Tamana [Reprint Author]; Tsutsui, Shusaku [Reprint Author]; Kiyohara, Tatsuya [Reprint Author]; Shinomura, Yasuhisa [Reprint Author]; Matsuzawa, Yuji [Reprint Author]
CORPORATE SOURCE: Osaka, Japan
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, ( 2003) Vol. 2003, pp. Abstract No. T1017. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of

Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003
AB Background & Aims: We previously reported that gastrin is capable of activating NF-kappaB through a protein kinase C (PKC)-dependent pathway in gastric epithelial cells. The present study was performed to determine which PKC isozyme is involved in gastrin receptor-mediated signals leading to activation of NF-kappaB. Methods: The cells used in the present study were MKGR26 cells created by transfecting gastrin receptor cDNA into MKN-28 gastric cancer cells and guinea pig isolated parietal cells. Phosphorylated PKC-' was detected by Western blot analysis. NF-kappaB transcriptional activity and binding activity were determined by luciferase assay using the pNF-kappaB-LUC containing five copies of consensus NF-kappaB site linked to a minimal E1B promoter-luciferase reporter gene and electrophoretic mobility shift analysis respectrively. Results: Gastrin induced activation of NF-kappaB in both MKGR26 cells and isolated parietal cells. The general PKC inhibitor GF109203X and rottlerin, an inhibitor of PKC-' and PKC-THETA, inhibited gastrin-induced DNA-protein complex formation in MKN-28 cells and guinea pig isolated parietal cells, while HBDDE, an inhibitor of PKC-alpha and PKC-gamma, had no effect on the complex formation. Rottlerin also inhibited the gastrin-induced transcriptional activity of NF-kappaB in MKGR26 cells, while Go6976, an inhibitor of PKC-alpha and PKC-beta, had no effect on this process. Introduction of the dominant negative PKC-' into MKGR26 cells abrogated gastrin-stimulated NF-kappaB activation, while the dominant negative PKC-THETA had no effect. Gastrin induced phosphorylation of PKC-' in MKGR26 cells within 5 minutes and the phosphorylation remained for over 60 minutes. Forced expression of wild-type PKC-' alone induced NF-kappaB activation in MKGR26 cells, which was inhibited by co-transfection of the dominant negative mutant of TRAF6, NIK or IKKs. Conclusions: PKC' plays a pivotal role in gastrin-induced activation of NF-kappaB in gastric epithelial cells..

L5 ANSWER 28 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:431940 BIOSIS
DOCUMENT NUMBER: PREV200200431940
TITLE: Lipopolysacchride induction of cyclooxygenase-2 expression is mediated via mitogen-activated protein kinase and nuclear factor-kB pathways in canine tracheal smooth muscle cells.
AUTHOR(S): Yang, Chuen-Mao [Reprint author]
CORPORATE SOURCE: Pharmacology, Chang Gung University, 259 Wen-Hwa 1 Road Kwei-San, Tao-Yuan, 3332, Taiwan
SOURCE: FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A1147. print.
Meeting Info.: Annual Meeting of Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 2002
Last Updated on STN: 14 Aug 2002

AB Lipopolysacchride (LPS) was found to induce inflammatory responses in the airways through PG synthesis. This study was to determine the mechanism of LPS-enhanced COX-2 expression associated with PGE2 synthesis in TSMCs. LPS increased COX-2 expression and PGE2 formation in a time- and concentration-dependent manner. COX-2 expression and PGE2 formation in response to LPS were attenuated by genistein, D609, U73122, GF109203X, staurosporine, removal of Ca2+ by addition of BAPTA/AM plus EGTA, LY294002, and wortmannin. Furthermore, LPS-induced activation of NF-kB correlated with the degradation of IkB-alpha in TSMCs. LPS-induced NF-kB activation, COX-2 expression, and PGE2 synthesis was inhibited by the dominant negative mutants of NIK and IKK-alpha, but not by IKK-beta. LPS-induced COX-2 expression and PGE2 synthesis were completely inhibited by PD98059 and SB203580, but these two inhibitors had no effect on LPS)-induced NF-kB activation, indicating that activation of p42/44 and p38 MAPK and NF-kB signaling pathways were independently required for these responses. These findings suggest that the increased expression of COX-2 correlates with the release of PGE2 from LPS-challenged TSMCs, at least in part, independently mediated through MAPKs and NF-kB signaling pathways in canine TSMCs. IL-1beta-mediated responses were modulated by PLC, Ca2+, PKC, tyrosine kinase, and PI3-K in these cells.

L5 ANSWER 29 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:447244 BIOSIS
DOCUMENT NUMBER: PREV200100447244
TITLE: Inhibitor of the inflammatory response induced by the TNFA and IL-1.
AUTHOR(S): Greene, Warner C. [Inventor]; Lin, Xin [Inventor, Reprint author]; Gelezuinas, Romas [Inventor]
CORPORATE SOURCE: San Francisco, CA, USA
ASSIGNEE: The Regents of the University of California
PATENT INFORMATION: US 6265538 20010724
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 24, 2001) Vol. 1248, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002
AB The present invention provides the molecular basis for cytokine induction of NF-kappaB-dependent immune and inflammatory responses, emphasizing a role for both NIK-NIK and NIK-IKK protein-protein interactions. A relatively small region of NIK selectively impairs the NIK-IKK interaction. The present invention provides a highly specific method for modulating NF-kappaB-dependent immune, inflammatory, and anti-apoptotic responses, based on interruption of the critical protein-protein interaction of NIK and IKK. The present invention provides methods for inhibiting NF-kappaB-dependent gene expression, using mutant NIK proteins. One embodiment of the present invention provides kinase-deficient NIK mutant proteins that inhibit activation of IKK. Another embodiment of the invention provides N-terminus NIK mutant proteins that bind IKK, thus inhibiting NIK/IKK interaction.

L5 ANSWER 30 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:244372 BIOSIS
DOCUMENT NUMBER: PREV200100244372
TITLE: The rotavirus VP4 protein directs cellular transcription by engaging a TRAF2-NIK signaling pathway.
AUTHOR(S): Mackow, Erich R. [Reprint author]; Kocer, Salih [Reprint

author]; Geimonen, Erika [Reprint author]; LaMonica, Rachel
CORPORATE SOURCE: HSC, SUNY at Stony Brook, T17 Rm048, Stony Brook, NY, 11794-8173, USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A907. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

AB Rotaviruses rapidly activate NF-kappaB and induce chemokine secretion following infection of intestinal epithelial cells (IECs). In IECs, NF-kappaB activation is effected through cytoplasmic signaling pathways requiring TNF Receptor Associated Factor 2 (TRAF2) (1). The ability of rotavirus particles which lack genomic RNA to activate NF-kappaB suggested that protein components of the rotavirus virion could direct cellular signaling. The rotavirus capsid protein VP4, and its' N-terminal VP8* cleavage product, contains TRAF binding motifs which are conserved among rotaviruses and only present in viral VP4 proteins. We have determined that cellular TRAFs (1, 2 and 3) are bound by the rhesus rotavirus (RRV) VP8* protein through three discrete TRAF-binding domains. Expression of either VP4 or VP8* selectively induces a 5-7 fold increase in NF-kappaB activity and synergistically enhances TRAF2 mediated NF-kappaB activation. Mutagenesis of VP8* TRAF binding motifs abolished VP8* binding to TRAFs and the ability of the protein to activate NF-kappaB. Expression of pathway specific dominant negative (DN) inhibitors, DN-TRAF2 or DN-NF-kappaB Inducing Kinase (DN-NIK), also abolished VP8*-, VP4- or rotavirus-mediated NF-kappaB activation. These findings demonstrate that rotavirus primarily activates NF-kappaB through a TRAF2-NIK signaling pathway and that VP4 and VP8* direct pathway activation through interactions with cellular TRAFs. Additional transcriptional reporters (AP-1, SRE and CRE) were not activated by VP8* or rotavirus infection suggesting that rotaviruses selectively elicit NF-kappaB-directed transcriptional responses. These results establish that fully cytoplasmic rotaviruses regulate cellular transcription by selectively engaging a TRAF2 signaling pathway of NF-kappaB activation. This suggests that rotaviruses direct specific cellular responses which could contribute to viral pathogenesis or host immunity.

L5 ANSWER 31 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:525188 BIOSIS
DOCUMENT NUMBER: PREV200100525188
TITLE: Hydrogen peroxide-mediated inhibition of lipopolysaccharide-stimulated inhibitory kappa B kinase activity in rat aortic smooth muscle cells.
AUTHOR(S): Torrie, Lindsay J.; MacKenzie, Christopher J.; Paul, Andrew; Plevin, Robin [Reprint author]
CORPORATE SOURCE: Department of Physiology and Pharmacology, Strathclyde Institute for Biomedical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow, G4 0NR, UK
r.plevin@strath.ac.uk
SOURCE: British Journal of Pharmacology, (September, 2001 ) Vol. 134, No. 2, pp. 393-401. print.
CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Nov 2001

Last Updated on STN: 23 Feb 2002

AB 1 In rat aortic smooth muscle cells (RASMC), exposure to lipopolysaccharide (LPS) resulted in NF-kappaB-DNA binding, degradation of IkappaB-alpha, -beta and -epsilon and increased activity of both alpha and beta isoforms of inhibitory kappa B kinase (IKK). 2 Expression of dominant-negative (DN)-IKK-alpha, IKK-beta and NF-kappaB-inducing kinase (NIK) abolished LPS-stimulated NF-kappaB reporter activity, suggesting that activation of a NIK /IKK-dependent pathway is indispensable for NF-kappaB activation by LPS in this cell type. 3 The tyrosine phosphatase inhibitor, pervanadate, abolished LPS-stimulated NF-kappaB-DNA-binding activity. However, the effect of pervanadate was shown to be mediated by excess hydrogen peroxide (H2O2) present in the reaction mix. Preincubation of RASMC with H2O2 inhibited LPS-stimulated IKK kinase activity and downstream NF-kappaB-DNA binding activity. 4 H2O2 also strongly stimulated p38 MAP kinase activity in RASMCs. Effective inhibition of this pathway using SB203580 did not reverse the effects of H2O2 on LPS-stimulated IKK/NF-kappaB signalling. 5 These studies show that hydrogen peroxide-mediated inhibition of LPS-stimulated NF-kappaB activation in RASMC occurs upstream of IKK. The inhibitory effect of H2O2 is not due to tyrosine phosphatase inhibition, it is mediated by H2O2 through a mechanism which is independent of any cross-talk involving MAP kinase homologues.

L5 ANSWER 32 OF 45 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:336258 BIOSIS
DOCUMENT NUMBER: PREV199900336258
TITLE: Curcumin, a dietary product, blocks cytokine mediated NF-kappaB activation and proinflammatory gene expression in intestinal epithelial cells by inhibiting IKK activity without directly affecting NF-kappaB-inducing kinase (NIK) or IGkappaB kinase (IKK).
AUTHOR(S): Jobin, Christian [Reprint author]; Bradham, C. A. [Reprint author]; Narula, A. S. [Reprint author]; Brenner, D. A. [Reprint author]; Sartor, R. B. [Reprint author]
CORPORATE SOURCE: Univ of North Carolina, Chapel Hill, NC, USA
SOURCE: Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A743. print.
Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association. Orlando, Florida, USA. May 16-19, 1999. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Aug 1999
Last Updated on STN: 24 Aug 1999

L5 ANSWER 33 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2004:787970 CAPLUS
DOCUMENT NUMBER: 141:374550
TITLE: Inhibition of ICAM-1 gene expression, monocyte adhesion and cancer cell invasion by targeting IKK complex: molecular and functional study of novel α-methylene-γ-butyrolactone derivatives
AUTHOR(S): Huang, Wei-Chien; Chan, Shu-Ting; Yang, Tzu-Lin; Tzeng, Cherng-Chyi; Chen, Ching-Chow
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, National Taiwan University, Taipei, 10018, Taiwan

SOURCE: Carcinogenesis (2004), 25(10), 1925-1934
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The transcription factor nuclear factor-kappaB (NF-κB) is a regulator related to cellular inflammation, immune responses and carcinogenesis. Therefore, components of the NF-κB-activating signaling pathways are frequent targets for the anti-inflammatory and anticancer agents. In this study, CYL-19 s and CYL-26z, two synthetic α-methylene-γ-butyrolactone derivs., were shown to inhibit the tumor necrosis factor-alpha (TNF-α)-induced intercellular adhesion mol.-1 (ICAM-1) expression in human A549 alveolar epithelial cells and the adhesion of U937 cells to these cells. RT-PCR anal. also demonstrated their inhibitory effects on TNF-α-induced ICAM-1 mRNA expression. TNF-α-induced ICAM-1 and NF-κB-dependent promoter activities were attenuated by CYL-19 s and CYL-26z. ICAM-1 promoter activities induced by the over-expression of wild-type NF-. kappa.B-inducing kinase and IκB kinase β (IKKβ) were also inhibited by both compds. Furthermore, CYL-19 s and CYL-26z inhibited the TNF-α-induced phosphorylation and degradation of IκBα and NF-κB-specific DNA-protein binding activity via targeting IKK complex directly, without any effect on the activations of other kinases such as ERK1/2 and p38. In addition to ICAM-1 expression, CYL-19 s and CYL-26z also suppressed other NF-κB-mediated gene expressions such as matrix metalloproteinase-9 (MMP-9) mRNA and cyclooxygenase-2 (COX-2) protein. In Matrigel assays, ICAM-1 and COX-2 expressions induced by TNF-α elicited A549 and NCI-H292 cell invasion, resp., and these effects were inhibited by both compds. In summary, our data demonstrated that CYL-19 s and CYL-26z down-regulate the TNF-α-induced inflammatory genes expression through suppression of IKK activity and NF-κB activation. These agents may be effective in the anti-inflammatory and anticancer therapy.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 34 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2004:714326 CAPLUS
DOCUMENT NUMBER: 141:378789
TITLE: Role of NF-κB and p38 MAP Kinase Signaling Pathways in the Lipopolysaccharide-Dependent Activation of Heme Oxygenase-1 Gene Expression
AUTHOR(S): Wijayanti, Nastiti; Huber, Sebastian; Samoylenko, Anatoly; Kietzmann, Thomas; Immenschuh, Stephan
CORPORATE SOURCE: Institut fuer Klinische Chemie und Pathobiochemie, Justus-Liebig-Universitaet Giessen, Giessen, D-35392, Germany
SOURCE: Antioxidants & Redox Signaling (2004), 6(5), 802-810
CODEN: ARSIF2; ISSN: 1523-0864
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Heme oxygenase (HO)-1 is the inducible isoform of the rate-limiting enzyme of heme degradation, which is up-regulated by a host of stress stimuli. The bacterial cell membrane component lipopolysaccharide (LPS) is a prototypical activator of monocytic cells. Here, it is shown that LPS induced the endogenous HO-1 gene expression in RAW264.7 monocytic cells. To investigate the mol. mechanisms of HO-1 gene induction by LPS, the authors performed transfection expts. with reporter gene constructs containing sequences of the proximal rat HO-1 gene promoter. Deletion and mutation

anal. indicated that a cAMP response element/activator protein-1 site (-664/-657), but not an E-box motif (-47/-42), played a major role for LPS-dependent HO-1 gene induction. Up-regulation of HO-1 promoter activity by LPS was decreased by pharmacol. nuclear factor-κB (NF-κB) inhibitors and by cotransfected expression vectors with dominant neg. isoforms of NF-κB-inducing kinase, inhibitor of NF-κB (IκB) kinase β, and IκBα. Moreover, the p38 mitogen-activated protein kinase (MAPK) inhibitor SB203580 and overexpressed dominant neg. p38β decreased, whereas dominant neg. p38δ increased, LPS-dependent induction of HO-1 gene expression. The results suggest that the NF-κB and p38 MAPK signaling pathways mediate the LPS-dependent induction of HO-1 gene expression via DNA sequences of the proximal promoter region.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 35 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 2003:613793 CAPLUS

DOCUMENT NUMBER: 140:52924

TITLE: Ursolic acid inhibits nuclear factor-κB activation induced by carcinogenic agents through suppression of IκBα kinase and p65 phosphorylation: correlation with down-regulation of cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D1

AUTHOR(S): Shishodia, Shishir; Majumdar, Sekhar; Banerjee, Sanjeev; Aggarwal, Bharat B.

CORPORATE SOURCE: Department of Bioimmunotherapy, Cytokine Research Laboratory, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Cancer Research (2003), 63(15), 4375-4383 CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The process of tumorigenesis requires cellular transformation, hyperproliferation, invasion, angiogenesis, and metastasis. Several genes that mediate these processes are regulated by the transcription factor nuclear factor-κB (NF-κB). The latter is activated by various carcinogens, inflammatory agents, and tumor promoters. Thus, agents that can suppress NF-κB activation have the potential to suppress carcinogenesis. Ursolic acid, a pentacyclic triterpene acid, has been shown to suppress the expression of several genes associated with tumorigenesis, but whether ursolic acid mediates its effects through suppression of NF-κB is not understood. In the study described in the present report, we found that ursolic acid suppressed NF-κB activation induced by various carcinogens including tumor necrosis factor (TNF), phorbol ester, okadaic acid, H2O2, and cigarette smoke. These effects were not cell type specific. Ursolic acid inhibited DNA binding of NF-κB consisting of p50 and p65. Ursolic acid inhibited IκBα degradation, IκBα phosphorylation, IκBα kinase activation, p65 phosphorylation, p65 nuclear translocation, and NF-κB-dependent reporter gene expression. Ursolic acid also inhibited NF-κB-dependent reporter gene expression activated by TNF receptor, TNF receptor-associated death domain, TNF receptor-associated factor, NF-κB-inducing kinase, IκBα kinase, and p65. The inhibition of NF-κB activation correlated with suppression of NF-κB-dependent cyclin D1, cyclooxygenase 2, and matrix metalloproteinase 9 expression. Thus, overall, our results indicate that ursolic acid inhibits IκBα kinase and p65

phosphorylation, leading to the suppression of NF-κB activation induced by various carcinogens. These actions of ursolic acid may mediate its antitumorigenic and chemosensitizing effects.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 36 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 2003:321568 CAPLUS
DOCUMENT NUMBER: 138:381120
TITLE: BRCA1 splice variants exhibit overlapping and distinct transcriptional transactivation activities
AUTHOR(S): McEachern, Kristen A.; Archey, William B.; Douville, Karen; Arrick, Bradley A.
CORPORATE SOURCE: Departments of Biochemistry and Medicine, Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Journal of Cellular Biochemistry (2003), 89(1), 120-132
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The global changes in gene expression induced by transient increased expression of full length BRCA1 as well as the spliced variant BRCA1S were evaluated by cDNA expression array in a human non-tumorigenic mammary epithelial cell line, MCF10A. Over 30 genes were identified that displayed an altered expression pattern in response to the expression of BRCA1 splice variants. The expression of NF. kappa.B inducing kinase was markedly down-regulated in BRCA1L transfected cells. However, a NFκB-responsive promoter construct yielded increased basal activity in BRCA1L transfected cells, as well as following treatment with tumor necrosis factor-α or lymphotoxin. In addition, nuclear exts. from BRCA1L transfected cells displayed increased DNA binding to the κB consensus site. The transcriptional activity of a panel of promoter constructs was evaluated following expression of wild type or mutant BRCA1. Full length BRCA1 transactivated the estrogen receptor-α (ERα) and BCL2 promoters as well as AP-1, SRE, and CRE containing promoters. Transactivation activity of the exon 11-deleted BRCA1S was more limited and usually of lower magnitude. The ability of a pathogenic mutation, 5382insC, to abrogate the transcriptional transactivation by BRCA1L and BRCA1S was also investigated. Mutant BRCA1 retained wild type levels of transcriptional activity for the ERα promoter as well as for the NFκB, AP-1, and CRE-responsive promoters but had reduced or no activity with the BCL2 and SRE promoters. These results show that BRCA1 isoforms have both overlapping and distinct transcriptional transactivation activity, and that a mutant form of BRCA1 implicated in carcinogenesis is not devoid of all activity.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 37 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 17

ACCESSION NUMBER: 2001:436389 CAPLUS
DOCUMENT NUMBER: 135:191720
TITLE: VP4 differentially regulates TRAF2 signaling, disengaging JNK activation while directing NF-κB to effect rotavirus-specific cellular responses
AUTHOR(S): LaMonica, Rachel; Kocer, Salih S.; Nazarova, Jennet; Dowling, William; Geimonen, Erika; Shaw, Robert D.; Mackow, Erich R.
CORPORATE SOURCE: Department of Medicine, Department of Molecular Genetics and Microbiology, State University of New York, Stony Brook, NY, 11794, USA

SOURCE: Journal of Biological Chemistry (2001), 276(23), 19889-19896
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rotaviruses rapidly activate NF-κB and induce the secretion of selected chemokines after infection. The ability of rotavirus particles lacking genomic RNA to activate NF-κB suggested that rotavirus proteins direct cell signaling responses. We identified conserved TNFR-associated factor (TRAF) binding motifs within the rotavirus capsid protein VP4 and its N-terminal VP8* cleavage product. TRAFs (-1, -2, and -3) are bound by the rhesus rotavirus VP8* protein through three discrete TRAF binding domains. Expression of VP4 or VP8* from rhesus or human rotaviruses induced a 5-7-fold increase in NF-κB activity and synergistically enhanced TRAF2-mediated NF-κB activation. Mutagenesis of VP8* TRAF binding motifs abolished VP8* binding to TRAFs and the ability of the protein to activate NF-κB. Expression of pathway-specific dominant neg. (DN) inhibitors DN-TRAF2 or DN-NF-.kappa.B -inducing kinase also abolished VP8*-, VP4-, or rotavirus-mediated NF-κB activation. These findings demonstrate that rotavirus primarily activates NF-κB through a TRAF2-NF-κB-inducing kinase signaling pathway and that VP4 and VP8* proteins direct pathway activation through interactions with cellular TRAFs. In contrast, transcriptional responses from AP-1 reporters were inhibited 5-fold by VP8* and were not activated by rotavirus infection, suggesting the differential regulation of TRAF2 signaling responses by VP8*. VP8* blocked JNK activation directed by TRAF2 or TRAF5 but had no effect on JNK activation directed by TRAF6 or MEKK1. This establishes that fully cytoplasmic rotaviruses selectively engage signaling pathways, which regulate cellular transcriptional responses. These findings also demonstrate that TRAF2 interactions can disengage JNK signaling from NF-κB activation and thereby provide a new means for TRAF2 interactions to determine pathway-specific responses.

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 38 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:293778 CAPLUS
DOCUMENT NUMBER: 139:67556
TITLE: Human RPE-monocyte co-culture induces chemokine gene expression through activation of MAPK and NIK cascade
AUTHOR(S): Bian, Zong-Mei; Elner, Susan G.; Yoshida, Ayako; Elner, Victor M.
CORPORATE SOURCE: Department of Ophthalmology, University of Michigan, Ann Arbor, MI, 48105, USA
SOURCE: Experimental Eye Research (2003), 76(5), 573-583
CODEN: EXERA6; ISSN: 0014-4835
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cell-cell contact between human retinal pigment epithelium (hRPE) cells and monocytes occurs in many retinal diseases involving blood-retinal barrier breakdown. This study investigates chemokine secretion induced by co-culture of hRPE cells and monocytes and illustrates the roles of p38 kinase, ERK1, JNK/SAPK and NF-κB-inducing kinase signaling pathways for hRPE IL-8 and MCP-1 secretion induced in hRPE by co-culture with monocytes. Co-culture of hRPE cells with monocytes increased steady-state IL-8 and MCP-1 mRNA and protein secretion. Stimulation of hRPE cells by

monocytes resulted in prominent increases in p38, ERK1/2 and JNK/SAPK phosphorylation, IκBα degradation, and NF-κB nuclear translocation. The induced IL-8 and MCP-1 proteins were almost completely suppressed by U0126, a specific mitogen-activated protein kinase kinase (MEK) inhibitor, or by SB203580, a selective p38 inhibitor. Chemokine secretion was completely blocked by simultaneous administration of U0126 and SB203580. Induction of IL-8 and MCP-1 was abrogated by Ro318220, an inhibitor of PKC, as well as by genistein or herbimycin A, inhibitors of PTK. In addition, anti-inflammatory drugs dexamethasone (DEX) and cyclosporin A (CSA) both blocked activation of JNKS/SAPK and the cell-cell contact induced production of hRPE IL-8 and MCP-1, while activation of p38 and ERK was only inhibited by DEX, but not by CSA. These results suggest that activation of DEX-sensitive, CSA-resistant MEK/ERK and p38 pathways, and activation of NF-κB, PKC, and PTK are essential for IL-8 and MCP-1 expression by hRPE cells.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 39 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:114033 CAPLUS
DOCUMENT NUMBER: 136:178935
TITLE: Antisense oligonucleotides inhibiting expression of the gene for HPK/GCK-like kinase
INVENTOR(S): Dean, Nicholas M.; Cowsert, Lex M.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 37 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6346416 | B1 | 20020212 | US 2000-651011 | 20000829 <-- |
| WO 2002018409 | A1 | 20020307 | WO 2001-US25860 | 20010817 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2001083443 | A | 20020313 | AU 2001-83443 | 20010817 <-- |

PRIORITY APPLN. INFO.: US 2000-651011 A 20000829
WO 2001-US25860 W 20010817

AB Antisense compds., compns. and methods are provided for modulating the expression of HPK/GCK-like kinase also known as NIK kinase. The compns. comprise antisense compds., particularly antisense oligonucleotides, targeted to nucleic acids encoding HPK/GCK-like kinase. Methods of using these compds. for modulation of HPK/GCK-like kinase expression and for treatment of diseases associated with expression of HPK/GCK-like kinase are provided. Effectiveness of antisense oligonucleotides was assayed by measuring kinase mRNA levels in cell cultures using real time PCR.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 40 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:467814 CAPLUS
DOCUMENT NUMBER: 135:225811

TITLE: Activation of p38, ERK1/2 and NIK Pathways is Required for IL-1β and TNF-α-induced Chemokine Expression in Human Retinal Pigment Epithelial Cells
AUTHOR(S): Bian, Zong-Mei; Elner, Susan G.; Yoshida, Ayako; Kunkel, Steven L.; Su, Jia; Elner, Victor M.
CORPORATE SOURCE: Department of Ophthalmology, University of Michigan, Ann Arbor, MI, USA
SOURCE: Experimental Eye Research (2001), 73(1), 111-121
CODEN: EXERA6; ISSN: 0014-4835
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chemokine secretion by human retinal pigment epithelium (hRPE) in response to IL-1β and TNF-α occurs in infectious and noninfectious retinal diseases. In this study, the roles of p38 kinase and extracellular signal-regulated kinase (ERK) signaling pathways were investigated for IL-1β- or TNF-α-induced IL-8 and MCP-1 secretion by hRPE cells. Treatment of hRPE cells with IL-1β or TNF-α caused increased steady-state IL-8 and MCP-1 mRNA levels and protein secretion. Stimulation of hRPE with IL-1β and TNF-α resulted in degradation of IκB-α, nuclear translocation of NF-κB, and prominent increases in p38 and ERK1/2 phosphorylation for as little as 3 min. The induced IL-8 and MCP-1 mRNA and proteins were partially suppressed by U0126, a specific MEK inhibitor, and by SB202190, a selective p38 inhibitor. This induction was completely blocked by simultaneous administration of the two drugs or by incubation with inhibitors for activation of NF-κB such as BAY11-7085, CAPE, and parthenolide. These results suggest that co-activation of MEK/ERK and p38 pathways as well as activation of NIK pathway are essential for IL-1β- and TNF-α-stimulation of IL-8 and MCP-1 gene expression in hRPE cells. Furthermore, co-administration of U0126 and SB202190 did not affect the induced degradation of IκB-α and NF-κB nuclear translocation, indicating that NF-κB is activated by IL-1β and TNF-α independently of activation of MEK/MAPK and p38 pathways in hRPE cells. (c) 2001 Academic Press.

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 41 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:566073 CAPLUS
DOCUMENT NUMBER: 131:198629
TITLE: A novel inhibitor of the inflammatory response induced by TNFα and IL-1
INVENTOR(S): Greene, Warner C.; Lin, Xin; Gelezuinas, Romas
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9943704 | A1 | 19990902 | WO 1999-US4110 | 19990225 <-- |
| W: AU, CA, JP | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| AU 9928778 | A | 19990915 | AU 1999-28778 | 19990225 <-- |
| US 6265538 | B1 | 20010724 | US 1999-257703 | 19990225 <-- |
| US 20020042499 | A1 | 20020411 | US 2001-871889 | 20010601 <-- |

US 6645728 B2 20031111
PRIORITY APPLN. INFO.: US 1998-76299P P 19980227
US 1999-257703 A3 19990225
WO 1999-US4110 W 19990225

AB The present invention provides the mol. basis for cytokine induction of NF-κB-dependent immune and inflammatory responses, emphasizing a role for both NIK-NIK (NIK is NF-κB-inducing kinase) and NIK-IKK (IKK is IκB-specific kinase) protein-protein interactions. A relatively small region of NIK selectively impairs the NIK-IKK interaction. The present invention provides a novel and highly specific method for modulating NF-κB-dependent immune, inflammatory, and anti-apoptotic responses, based on interruption of the critical protein-protein interaction of NIK and IKK. The present invention provides methods for inhibiting NF-κB-dependent gene expression, using mutant NIK proteins. One embodiment of the present invention provides kinase-deficient NIK mutant proteins that inhibit activation of IKK. Another embodiment of the invention provides N-terminus NIK mutant proteins that bind IKK, thus inhibiting NIK/IKK interaction.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 42 OF 45 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:407771 CAPLUS
DOCUMENT NUMBER: 131:153360
TITLE: Therapeutic Potential and Strategies for Inhibiting Tumor Necrosis Factor-α
AUTHOR(S): Newton, Robert C.; Decicco, Carl P.
CORPORATE SOURCE: Departments of Inflammatory Diseases Research and Chemical and Physical Sciences, Exp. Station, The DuPont Pharmaceuticals Company, Wilmington, DE, 19880-0500, USA
SOURCE: Journal of Medicinal Chemistry (1999), 42(13), 2295-2314
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 249 refs. on tumor necrosis factor-α (TNF) as a validated target for drug discovery. The authors objective is to move beyond compds. that are currently under study and, using data generated form both mechanistic and compound discovery research, identify sites amenable to the design of small-mol. therapeutics. Some of the targets discussed are NF-κB, the kinases NIK or IKK, mechanisms that link surface receptors to NIK, the regulation of TNF expression by cAMP modulation or MAP kinase inhibition, phosphodiesterases or p38 inhibition, gene regulation at the transcriptional level, any of the aspects of the TNF receptor-signaling complex (especially TRAF-2 or PEG3) or the regulation of TNF-induced gene expression by MAP kinase inhibition.

REFERENCE COUNT: 249 THERE ARE 249 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 43 OF 45 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004388694 EMBASE
TITLE: Tendon healing in vitro: Activation of NIK, IKKα, IKKβ, and NF-κB genes in signal pathway and proliferation of tenocytes.
AUTHOR: Tang, Jin Bo, Dr. (correspondence); Xu, Yan; Wang, Xiao Tian

CORPORATE SOURCE: jbtang@rics.bwh.harvard.edu
AUTHOR: Tang, Jin Bo, Dr. (correspondence); Xu, Yan; Wang, Xiao Tian
CORPORATE SOURCE: Hand Surgery Research Center, Department of Hand Surgery, Affil. Hosp. of Nantong Med. College. jbtang@rics.bwh.harvard.edu
AUTHOR: Tang, Jin Bo, Dr. (correspondence)
CORPORATE SOURCE: Gene Therapy and Tissue Engineering, Surgical Research-133 North Campus, Roger Williams Medical Center, 825 Chalkstone Avenue, Providence, RI 02908-4735, United States. jbtang@rics.bwh.harvard.edu
SOURCE: Plastic and Reconstructive Surgery, (May 2004)
Vol. 113, No. 6, pp. 1703-1711.
Refs: 35
ISSN: 0032-1052 CODEN: PRSUAS
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
022 Human Genetics
029 Clinical and Experimental Biochemistry
009 Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Sep 2004
Last Updated on STN: 30 Sep 2004
AB Initiation of DNA transcription and proliferation of tendon cells are critical to tendon healing and require pivotal signals to the nucleus. Exploring intracellular signaling pathways pertinent to the healing process may reveal new approaches to accelerating the healing rate of the tendon. The authors investigated expression of NIK, IKKα, IKKβ, and NF-κB genes in the signal pathway and tenocyte proliferation in an in vitro model in which cultured tenocytes were exposed to basic fibroblast growth factor (bFGF). Tenocytes were obtained from explant culture of rabbit intrasynovial tendons and were treated with bFGF at concentrations of 0, 2, or 10 ng/ml. Levels of expression of a series of genes for key factors along the signaling route-nuclear factor (NF)-.kappa.B-inducing kinase, inhibitor of kappa B kinase alpha and beta, and the NF-κB-were examined by quantitative analysis of products of reverse transcription and multiplex polymerase chain reactions. Proliferation of the cells was assessed with evaluation of growth curves and immunochemical labeling of the DNA of the cells. Expression levels of NIK, IKKα, IKKβ, and NF-κB genes were significantly increased by bFGF at concentrations of 2 and 10 ng/ml. Western blot confirmed the increase of NF-κB in the tenocytes. The proliferation rate of the cells was significantly promoted by bFGF. Expression of these genes increased proportionately to the amounts of bFGF stimulating the cells and was correlated with increases in the proliferation rate. This study showed that expression of a series of genes along the NF-κB pathway was remarkably promoted by bFGF. The effects were proportionate to in vitro cell proliferation rate. Results of the study suggest that activation of a series of genes along the NF-κB pathway may play a pivotal role in initiating cell proliferation during the healing process of intrasynovial tendons. As activation of genes in signal transduction pathways is a new field in the biology of growth factor action with tremendous potential in promoting tissue repairs, manipulation of expression of a series of genes along the NF-κB pathway can be a new target of enhancing tendon healing through molecular mechanisms.


ACCESSION NUMBER: 2003304406 EMBASE

TITLE: Stretch-induced IL-8 depends on c-Jun NH(2)-terminal and nuclear factor-κB-inducing kinases.
AUTHOR: Li, Li-Fu; Ouyang, Bin; Choukroun, Gabriel; Matyal, Robina; Mascarenhas, Marcella; Jafari, Behrouz; Bonventre, Joseph V.; Quinn, Deborah A. (correspondence)
CORPORATE SOURCE: Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, United States.
AUTHOR: Force, Thomas
CORPORATE SOURCE: Molec. Cardiology Research Institute, Department of Medicine, Tufts University School of Medicine, Boston, MA 02111, United States.
AUTHOR: Li, Li-Fu
CORPORATE SOURCE: Chang Gung University, Tao-Yuan 333, Taiwan, Province of China.
AUTHOR: Choukroun, Gabriel
CORPORATE SOURCE: Int. Med. and Nephrology Department, Amiens Hospital, 80054 Amiens, France.
AUTHOR: Quinn, Deborah A. (correspondence)
CORPORATE SOURCE: Mass. General Hospital, Pulmonary and Critical Care Unit, 55 Fruit St., Boston, MA 02114, United States.
SOURCE: American Journal of Physiology - Lung Cellular and Molecular Physiology, (1 Aug 2003) Vol. 285, No. 2 29-2, pp. L464-L475.
Refs: 45
ISSN: 1040-0605 CODEN: APLPE7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 2003
Last Updated on STN: 14 Aug 2003
AB Positive pressure ventilation with large tidal volumes has been shown to cause release of cytokines, including interleukin (IL)-8. The mechanisms regulating lung stretch-induced cytokine production are unclear. We hypothesized that stretch-induced IL-8 production is dependent on the activation of the mitogen-activated protein kinases, c-Jun NH(2)-terminal kinases (JNK), p38, and/or extracellular signal-regulated kinase (ERK) 1/2. We exposed A549 cells, a type II-like alveolar epithelial cell line, to cyclic stretch at 20 cycles/min for 5 min-2 h. Cyclic stretch induced IL-8 protein production, IL-8 mRNA expression, and JNK activation, but only transient activation of p38 and ERK1/2. Inhibition of stretch-induced JNK activation by adenovirus-mediated gene transfer of stress-activated protein kinase (SEK-1), a dominant-negative mutant of SEK-1, the immediate upstream activator of the JNKs, and pharmacological JNK inhibitor II SP-600125 blocked IL-8 mRNA expression and attenuated IL-8 production. Inhibition of p38 and ERK1/2 did not affect stretch-induced IL-8 production. Stretch-induced activation NF-κB and activator protein (AP)-1 was blocked by NF-κB inhibitor and JNK inhibitor, respectively. An NF-IL-6 site was not essential for cyclic stretch-induced IL-8 promoter activity. Stretch also induced NF -.kappa.B-inducing kinase ( NIK) activation, and inhibition of NF-κB attenuated IL-8 mRNA expression and IL-8 production. We conclude that stretch-induced transcriptional regulation of IL-8 mRNA and IL-8 production was via activation of AP-1 and NF-κB and was dependent on JNK and NIK activation, respectively.

ACCESSION NUMBER: 2002225762 EMBASE
TITLE: Differential requirement for NF-κB-inducing kinase in the induction of NF-κB by IL-1β, TNF-α, and Fas.
AUTHOR: Russo, Maria P.; Bennett, Brydon L.; Manning, Anthony M.; Brenner, David A.; Jobin, Christian (correspondence)
CORPORATE SOURCE: Div. of Digestive Diseases, Glaxo Bldg., Univ. of North Carolina, Chapel Hill, Chapel Hill, NC 27599-7038, United States. Job@med.unc.edu
SOURCE: American Journal of Physiology - Cell Physiology, ( 2002) Vol. 283, No. 1 52-1, pp. C347-C357.
Refs: 65
ISSN: 0363-6143 CODEN: AJPCDD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Jul 2002
Last Updated on STN: 11 Jul 2002

AB In this study, we examined the role of the nuclear factor-κB (NF-κB)-inducing kinase (NIK) in distinct signaling pathways leading to NF-κB activation. We show that a dominant-negative form of NIK (dnNIK) delivered by adenoviral (Ad5dnNIK) vector inhibits Fas-induced IκBα phosphorylation and NF-κB-dependent gene expression in HT-29 and HeLa cells. Interleukin (IL)-1β- and tumor necrosis factor-α (TNF-α)-induced NF-κB activation and κB-dependent gene expression are inhibited in HeLa cells but not in Ad5dnNIK-infected HT-29 cells. Moreover, Ad5dnNIK failed to sensitize HT-29 cells to TNF-αinduced apoptosis at an early time point. However, cytokine-and Fas-induced signals to NF-κB are finally integrated by the IκB kinase (IKK) complex, since IκBα phosphorylation, NF-κB DNA binding activity, and IL-8 gene expression were strongly inhibited in HT-29 and HeLa cells overexpressing dominant-negative IKKβ (Ad5dnIKKβ). Our findings support the concept that cytokine signaling to NF-κB is redundant at the level of NIK. In addition, this study demonstrates for the first time the critical role of NIK and IKKβ in Fas-induced NF-κB signaling cascade.

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SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 17:40:33 ON 24 SEP 2008